

Introduction

The characteristic signature of heterocyclic compounds is the presence of any heteroatom in place of carbon. They are the largest of the traditional divisions of organic chemistry and play a crucial role not only in the industrial and biological domains but also in the functioning of the human body.¹ They play an important role in the nervous system and biochemical processes such as biosynthesis in plants and animals.² In the human body, nucleobases such as adenine, thymine, guanine, cytosine, and uracil, as well as purine and pyrimidine are made-up with *N*-containing heterocyclic compounds. These nucleoside bases are the fundamental units of the genetic code, found in DNA and RNA.³ The energy-transfer molecules AMP, ADP, and ATP also contain nucleotide bases.⁴ Diverse organic compounds, such as hormones, vitamins, amino acids, hemoglobin, antibiotics, alkaloids, pigments, and numerous synthetic drugs containing heterocyclic moieties, have significant roles in human life (Figure 1.1).⁵ Therefore, heterocycles are ubiquitous and privileged structures due to their extensive use in the total synthesis of complex organic molecules as a building block⁶ and common motifs in the design of novel pharmaceuticals.⁷ Almost all known biologically and physiologically active organic compounds have at least one heterocyclic core and sixty percent of today's marketed drugs contain a minimum of one heterocycle motif. They possess a high affinity for metal ions, allowing them to form stable complexes.⁸ They are utilized in the creation of agrochemicals, including herbicides, insecticides, and fungicides.⁹ They have made significant contributions to the rise in agricultural productivity and the development of sustainable agricultural practices. They are used as precursors and building elements in materials science for the synthesis of polymers, dyes, and electronic materials.¹⁰ They have played a vital role in the development of new materials with enhanced electronic and optical properties, which have applications in photovoltaics, sensors, and light-emitting diodes, among others.¹¹

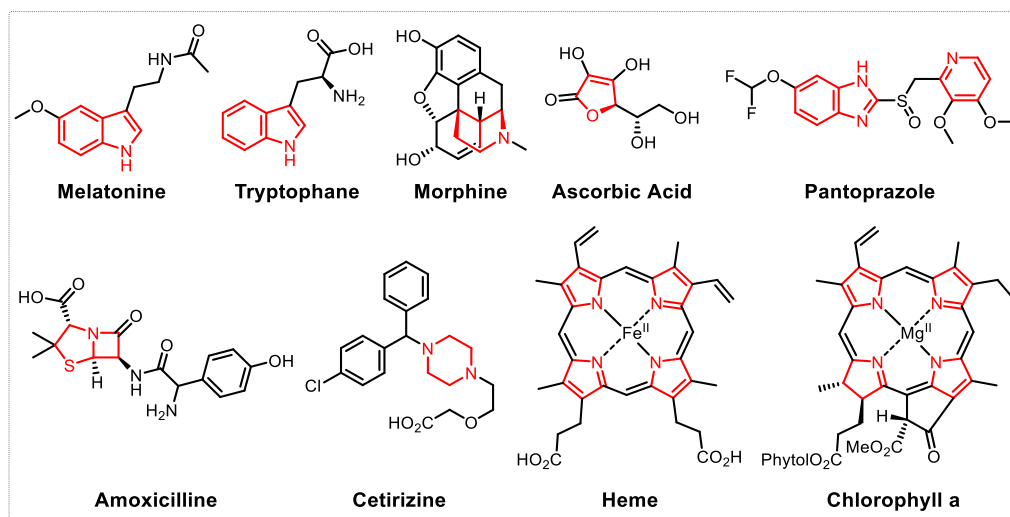


Figure 1.1: Selective examples of diverse heterocycles having significant roles in human life

An array of heterocyclic compounds with the most common heteroatoms, e.g., sulfur, nitrogen, and oxygen, are recognized as a unique building block for the synthesis of molecules with biological or medicinal importance.¹² Tremendous efforts have been directed towards the

synthesis of a library of diverse heterocycles and identifying as leads for developing new drugs.¹³ Several methods including transition-metal catalyzed,¹⁴ organocatalyzed,¹⁵ base-catalyzed,¹⁶ Lewis's acid-base catalyzed,¹⁷ radical initiated,¹⁸ and many more¹⁹ have been developed to synthesize these privileged scaffolds. Among the variety of heterocycles, tetrahydrothiophenes, α -pyrones, dihydroindoles, and benzoxazoles scaffolds have garnered the most attention due to their ubiquitous use in both academia and industry. They exhibit a variety of medicinal properties, including antibiotic, antidiabetic, antibacterial, antitumor, anti-HIV, anti-inflammatory, antidepressant, antimicrobial, antimalarial, antifungal, antiviral, hypnotic, vasopressor modifier agent, and cytotoxic effects. Also, they have major structural characteristics common to many natural products.²⁰⁻²² Several synthetic and natural compounds having these scaffolds are already being tested in pre-clinical trials for the treatment of several disorders.²³

On the other hand, one of the major challenging tasks in synthetic chemistry is the establishment of a one-pot approach for the synthesis of complex heterocycles. It requires precise assessment of a number of variables, like the choice of suitable reaction conditions, the optimization of reaction parameters, and the management of reaction selectivity. It also demands an in-depth understanding of the underlying reaction mechanisms as well as the capacity to regulate the reactivity and selectivity of each individual reaction stage. Despite these challenges, cascade approaches have made significant advancements over the past 20 years particularly in the area of organocatalysis for developing novel and efficient routes with a minimum number of operations for synthesizing complex molecules.²⁴ These reactions represent not only the multiple bond-forming transformations but also the subsequent reactions in which the functionalities created in the earlier steps are manifested. It enables the incorporation of multiple functional groups and stereocenters into a single molecule in a reaction sequence. Cascade approaches have several advantages over traditional stepwise synthesis, including fewer reaction steps, reduced time, and increased overall efficiency of processes by reducing physical effort as well as minimizing the use of solvents and chemicals.²⁴

In recent decades, a huge spike in the use of solid-supported catalysts/reagents in synthetic chemistry because of their enormous significance in both academic and industry.²⁵ A family of catalysts known as solid-supported catalysts is immobilized on solid supports like silica, alumina, or zeolites. They have several advantages over traditional homogeneous catalysts, including recyclability, improved stability, enhanced selectivity and efficiency, simplify the purification step, and these make the approaches more sustainable by reducing the overall cost.²⁵ Also, they have ability to use as catalysts in continuous flow systems.²⁶ Therefore, they have become an essential tool in the creation of sustainable chemical processes.

The main emphasis of this thesis is to development of sustainable one-pot cascade approaches for constructing multifunctional diverse heterocycles having tetrahydrothiophene, α -pyrone, dihydroindole, and benzoxazole skeletons form easily accessible synthons. Herein, we have reviewed some selective reports on the organocatalyzed synthesis of these heterocycles in this chapter.

1.1 BRIEF LITERATURE REVIEW FOR THE SYNTHESIS OF TETRAHYDROTHIOPHENES

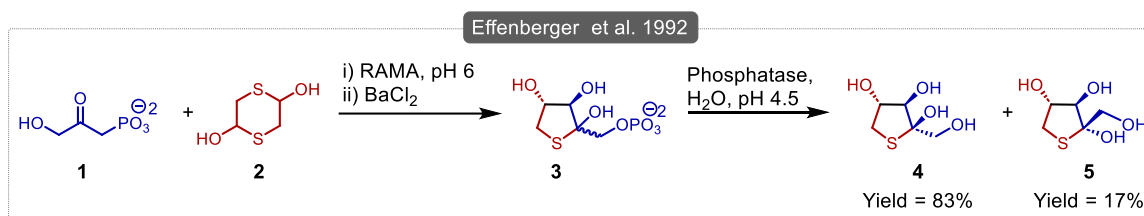
Both natural and synthetic organosulfur compounds have significant biological and medicinal properties.²⁷ Tetrahydrothiophenes (THTs) are one of the sulfur-containing heterocyclic compounds that find extensive application in various industries, including pharmaceuticals, agrochemicals, and materials science.²⁸ Its unique structure is characterized by a five-membered ring containing a saturated sulfur heterocycle made up of four sp^3 hybridized carbon atoms and one sulfur atom. They have specific chemical and physical properties that make them valuable building blocks in organic synthesis. THT has garnered significant interest among researchers aiming to develop efficient and selective methods for its production. Researchers continually explore new strategies and modifications to existing methodologies to improve the

efficiency, atom economy, and environmental sustainability for the synthesis of substituted THTs. Direct methods²⁹ involve transition metal-catalyzed reactions, organocatalyzed, base-catalyzed, and NHC-catalyzed reactions and indirect strategies³⁰ utilize hydrogenation, desulfurization, and ring-closing reactions. This literature report provides a brief overview of different synthetic approaches employed in the synthesis of tetrahydrothiophene via metal-free catalysis/organocatalysis.

1.1.1 Michael/Aldol Reactions

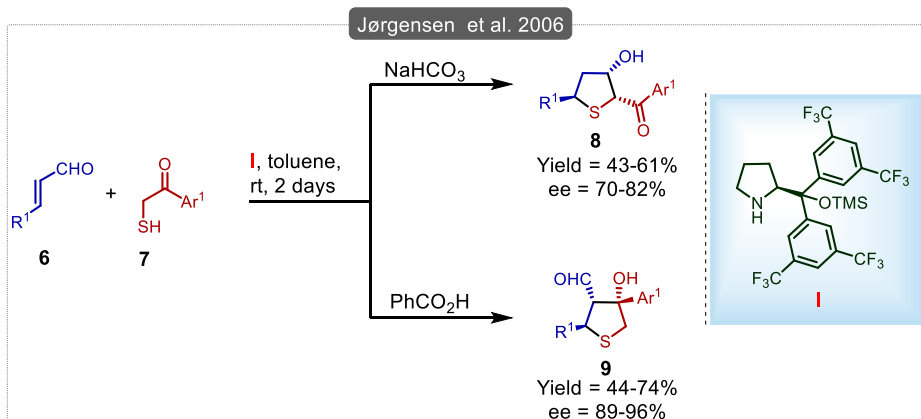
The thia-Michael/aldol cascade reaction is one of the frequently explored and powerful synthetic methods to constructing tetrahydrothiophenes. It involves the conjugate addition of a suitable nucleophile, like thiol or dithiane diol, to activated olefins, typically an α,β -unsaturated carbonyl compounds, in the presence of an acid or base catalyst. Further, the intermediate undergoes intramolecular cyclization via the aldol process to produce the tetrahydrothiophene ring. In the last two decades, several organo- and metal-catalyzed Michael/aldol reactions have been successfully developed to construct THTs.²⁹

In 1992, Effenberger and colleagues described a method for the synthesis of thiosugars (**4** and **5**) via rabbit muscle aldolase (RAMA) catalyzed reaction of 1,4-dithiane-2,5-diol **2** with dihydroxyacetone phosphate **1** (Scheme 1.1).³¹ This was likely the first time that 2-marcaptoacetaldehyde was used to synthesize substituted tetrahydrothiophenes.



Scheme 1.1: RAMA catalyzed synthesis of tetrahydrothiophenes

Jørgensen and co-workers have developed the first straightforward organocatalytic cascade approach for the synthesis of functionalized optically active THTs in 2006.³² The reaction relies on the Michael-aldol domino process of thiol **7** to α,β -unsaturated aldehydes **6**. In this report, two different regioisomeric products were formed by the use of different additives, benzoic acid or NaHCO_3 , from the same starting materials (Scheme 1.2). Both THT derivatives were obtained in moderate to good yields with high selectivity. Further, the stereochemical consequence of these reactions were examined. A plausible mechanism for these organocatalytic cascade approach is presented in Figure 1.2.



Scheme 1.2: Regio-divergent Synthesis of tetrahydrothiophenes through iminium catalysis

Catalyst **I** first activates the aldehyde **6** to produce an iminium ion intermediate **A**. The nucleophilic addition of the thiol at the β -carbon to of iminium took place via *Re*-face attack to produce (*R*)-configured enamine **B**. Enamine **B** is then tautomerized to form iminium ion **C**, which upon hydrolysis produced the thioether **D** and regenerate the catalyst. Then, thioether **D** is enolized to make enol, which undergoes regiospecific aldol cyclization to produce tetrahydrothiophene **8**. Presumably, no asymmetric induction occurs with catalyst **I** during this cyclization process. On the other hand, benzoic acid prevents the hydrolysis process, ensuring the survival of enamines **B**. The enamine further undergoes a facile diastereoselective intramolecular aldol-like reaction to produce iminium ions **E**, followed by hydrolysis leading to the formation of THT **9**.

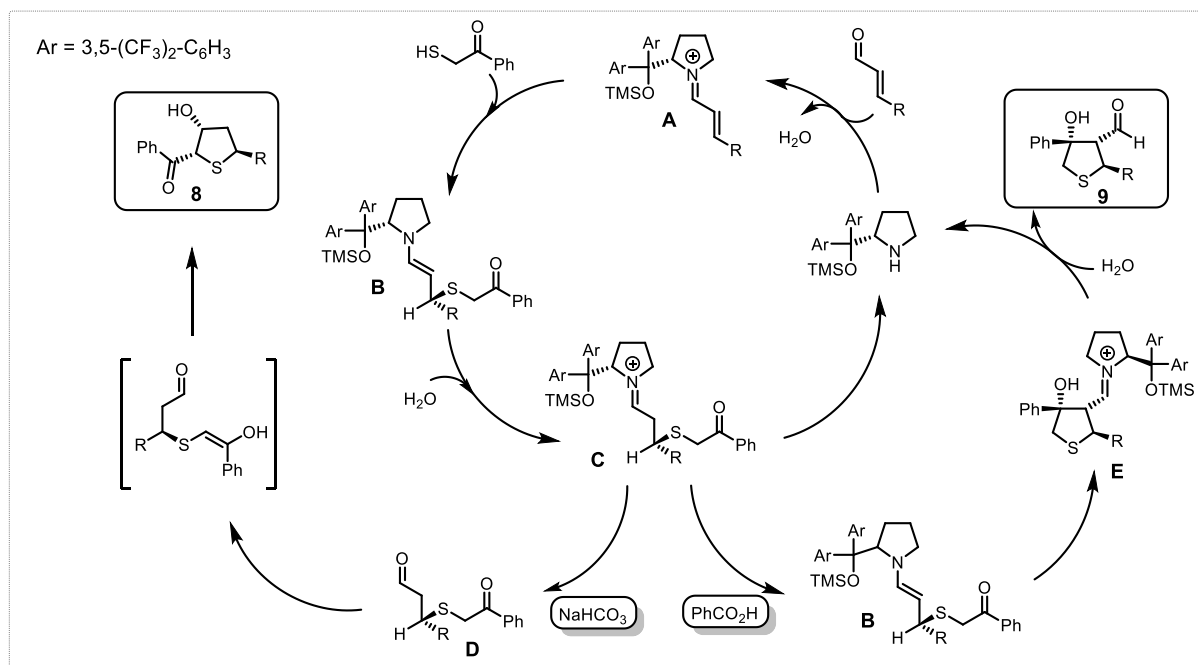
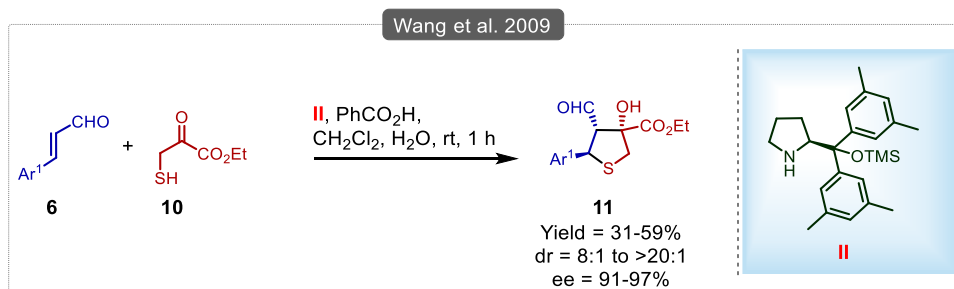


Figure 1.2: Mechanism of domino Michael-aldol synthesis of optically active THTs

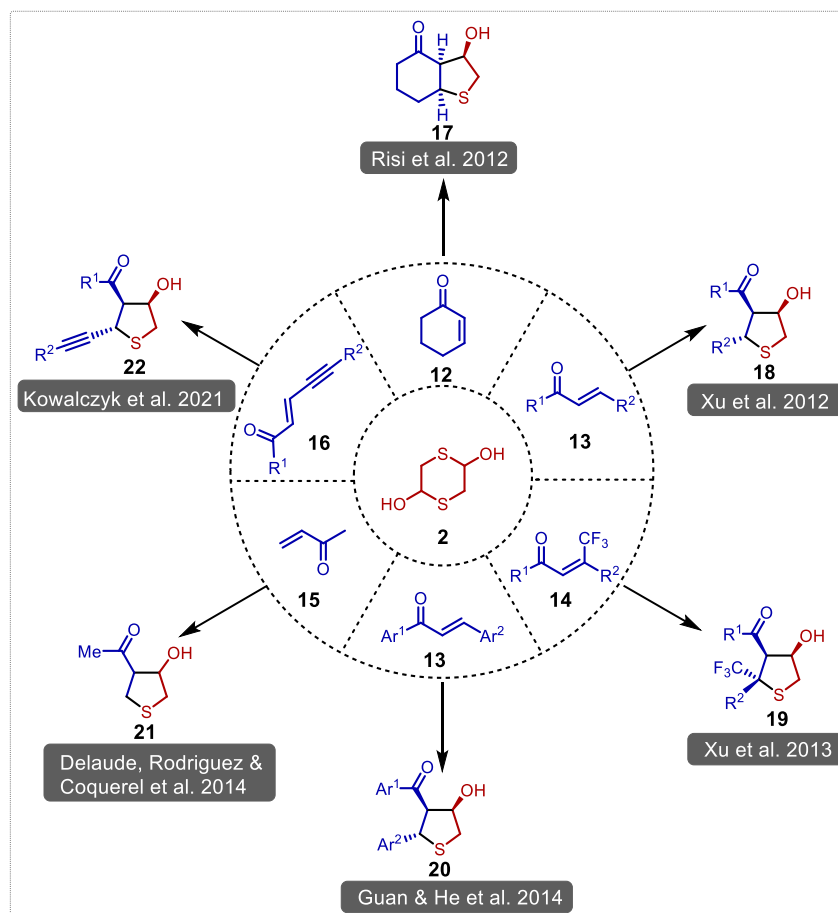
In 2009, Wang's group developed almost similar methodology with the use of different sulfa-partner **10** and proline-derived catalyst **II** (Scheme 1.3). They have used ethyl-3-mercapto-2-oxopropionate as a Michael donor and *trans*-cinnamaldehyde as a Michael acceptor for the cascade approach.³³ The desired THTs **11** were isolated in moderate yield and high diastereo- and enantio-selectivities. Benzoic acid as an additive is used in this cascade approach.



Scheme 1.3: Proline-derived amine catalyzed synthesis of THTs

Several research groups have developed the Michael addition/aldol reaction sequence for the construction of multi-substituted tetrahydrothiophenes by using 1,4-dithiane-2,5-diol **2** as a sulfa-partner with various substituted activated olefins (Scheme 1.4). In 2012, C. D. Ris reported a base-catalyzed one-pot racemic synthesis of substituted THTs through Michael/aldol reaction.³⁴ They also showed the synthesis of nitro-substituted THTs in good yield via the

Michael/Henry reaction of in-situ generated nitro alkenes with mercaptoacetaldehyde (Scheme 1.8).



Scheme 1.4: Synthesis of multi-substituted THTs via Michael/aldol reaction of several activated alkenes with 1,4-dithiane-2,5-diol

In the same year, Xu et al. have demonstrated a bifunctional squaramide catalyzed thia-Michael/aldol reaction of chalcones **13** with 1,4-dithiane-2,5-diol **2**.³⁵ Desired THTs were obtained in highly stereo-controlled fashion with low catalyst loading. The synthesized THTs have three contiguous stereogenic centers. The catalytic cycle of this hydrogen-bond-mediated cascade approach is depicted in Figure 1.3. In this, the bifunctional squaramide could synergistically activate both nucleophile mercaptoacetaldehyde **2** and electrophile **13**. The activation modes are shown by model **A**. The catalyst-assisted sulfa-Michael addition followed by an intramolecular aldol process affords the desired THT. Further, the absolute configuration was identified as (2*R*, 3*S*, 4*S*) of a product by X-ray crystallographic analysis. In the next year, the same research group disclosed another method utilizing β-aryl-β-trifluoromethylated enones **14** as an electrophile to construct quaternary carbon-bearing trifluoromethylated THTs **19**.³⁶ The reaction was catalyzed by *Cinchona* derived bifunctional squaramide. In 2014, Zhi Guan and Yan-Hong He described an efficient, environment-friendly, catalyst-free thia-Michael/aldol cascade synthesis of THTs utilizing water as a green solvent. Further, the method was extended to cascade thia-Michael/Henry reactions leading to 3-nitro-substituted THTs (Scheme 1.8).³⁷ Importantly, the utilization of water as a solvent in this cascade approach provides not only a greener methodology but also provides a unique property for the formation of a particular diastereoisomer. In the same year, NHC catalyzed Carba-, Sulfa-, and Phospha-Michael addition reaction was developed.³⁸ Utilizing this approach, corresponding tetrahydrothiophenes **21** were synthesized in excellent yield with moderate diastereoselectivity by the reaction of 1,4-dithiane-2,5-diol **2** and methyl vinyl ketone **15** in the presence of imidazol(in)ium-2-carboxylate. This catalyst made it possible to efficiently perform a variety of Michael additions without an

obligation for an external strong base and the NHC was obtained by deprotonating an azolium salt. Recently, Kowalczyk groups have developed a *Cinchona*-derived squaramide-catalyzed asymmetric cascade thia-Michael/aldol reaction of activated olefins.³⁹ The reaction has relied on the stereoselective addition of mercaptan to Michael acceptor to form a sulfide, followed by an intramolecular aldol reaction that led to three contiguous stereocenters bearing chiral THTs. The developed method was found to be efficient with multiple Michael acceptors to access corresponding THTs in excellent yields and stereoselectivities. Further, the multifaceted roles of catalysts to illuminate the chirality transfer mechanism and the stereochemical outcome was shown by KS-DFT calculations.

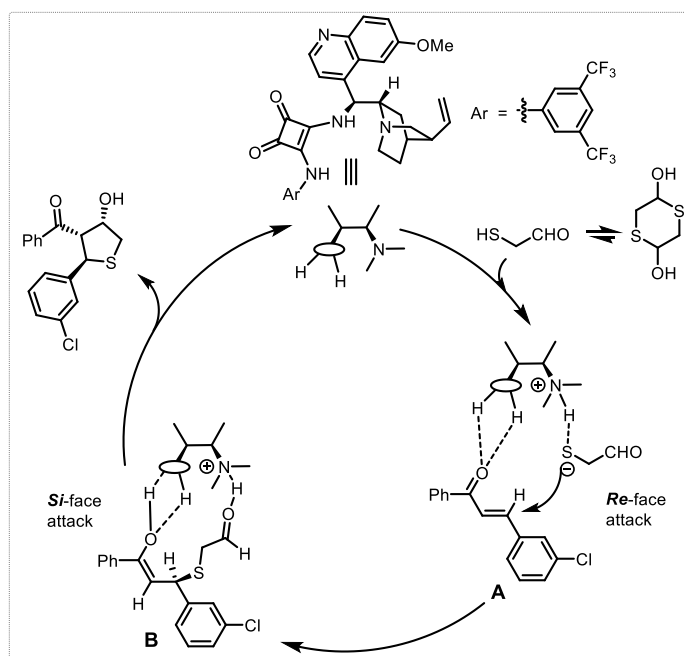
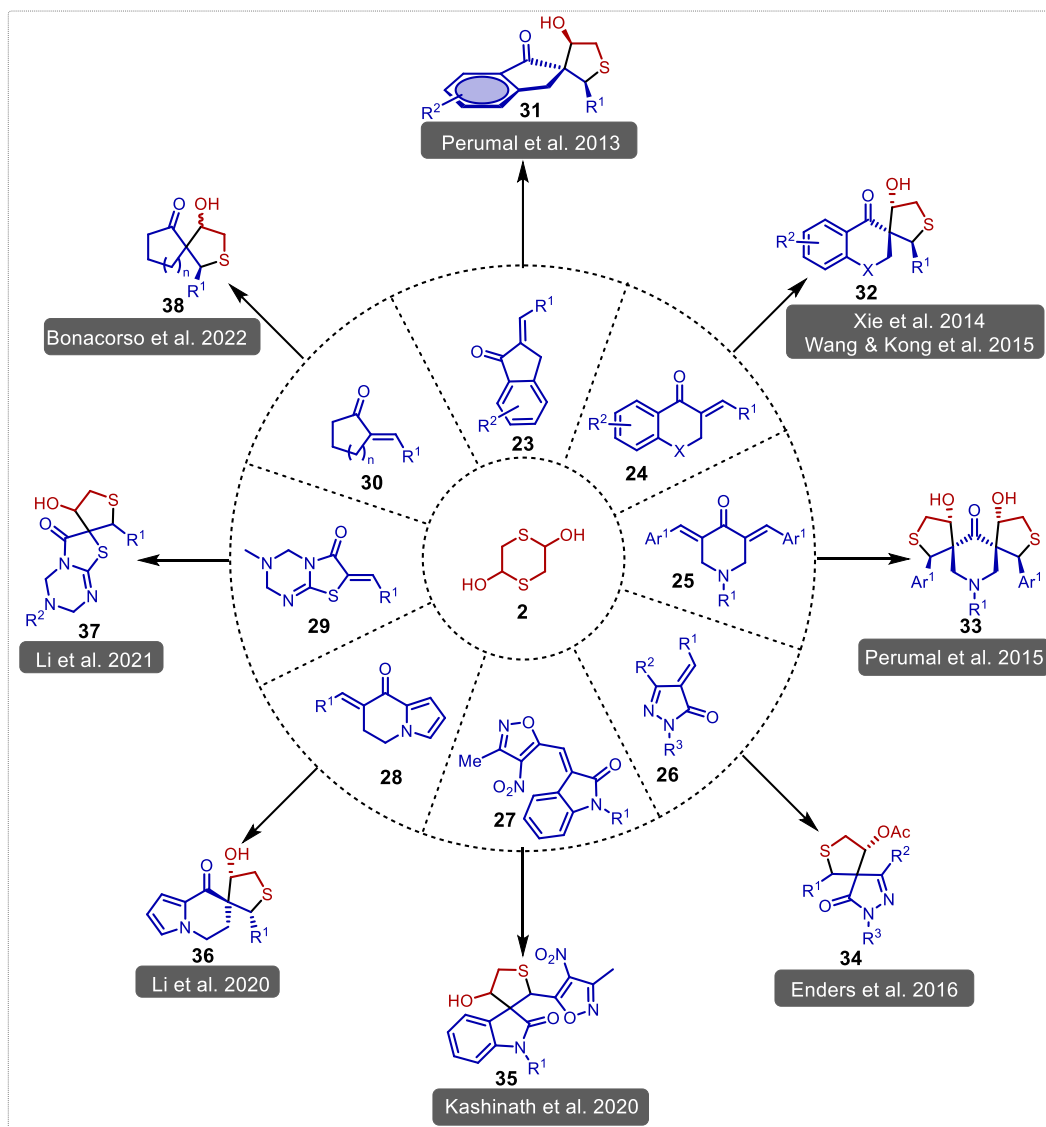


Figure 1.3: Catalytic Cycle for hydrogen-bond mediated Sulfa-Michael/Aldol Cascade Reaction

Besides the synthesis of THTs, many research groups have devised the Michael addition/aldol reaction sequence for the production of spiro-tetrahydrothiophenes (Scheme 1.5) by employing the same precursor i.e., 1,4-dithiane-2,5-diol with various activated olefins. In 2013, S. Perumal et al. disclosed an atom-efficient and eco-friendly domino reaction of substituted dihydro-1*H*-inden-1-ones **23** with dithiane-diols to afford spiro[indene-2,3'-thiophen]-1(3*H*)-one derivatives **31**.^{40a} In the next year, Xie's group reported catalyst-free synthesis of polyheterocyclic spiro-tetrahydrothiophene **32** derivatives from readily available chalcones and dithiane-diols. Furthermore, they have demonstrated the synthesis of chiral spiro-THTs in the presence of a PTC catalyst with the same starting material.⁴¹ Perumal's group developed another domino Michael/aldol reaction of bis(arylidene)piperidine-4-ones **25** and dithiane-diols **2** to synthesize bis-spiropiperidone-THTs **33**.^{40b} Importantly, the cascade reaction proceeded via two annulations each involving Michael addition followed by intramolecular aldol sequence resulting the construction of four new bonds, two C-C and two C-S, in a one-pot. In 2015, Wang and Kong et al. established a facile approach to synthesize spiro-chromanone-tetrahydrothiophenes **32** via a thia-Michael/aldol cascade reaction.⁴² The relative stereochemistry of products was confirmed by HMBC and ROESY correlations spectroscopy. Next year, Enders et al. demonstrated DIPEA catalyzed diastereoselective synthesis of spiro-pyrazolone-THTs **34**.⁴³ After the formation of spiro-THTs, the hydroxy group of the product **34** was converted to an ester in situ. Furthermore, the asymmetric version of the developed method was also tested. However, a maximum 23% of enantioselectivity was obtained with *Cinchona* derived chiral bifunctional squaramide catalyst. In 2019, Kashinath et al. developed the catalyst-free regioselective synthesis of spiro-isoxazole-oxindole-THTs **35** from the cascade reaction of isoxazole-isatin styrene **27** with dithiane-diols.⁴⁴ Interestingly, the cascade reaction proceeded through 1,4-conjugate addition followed by

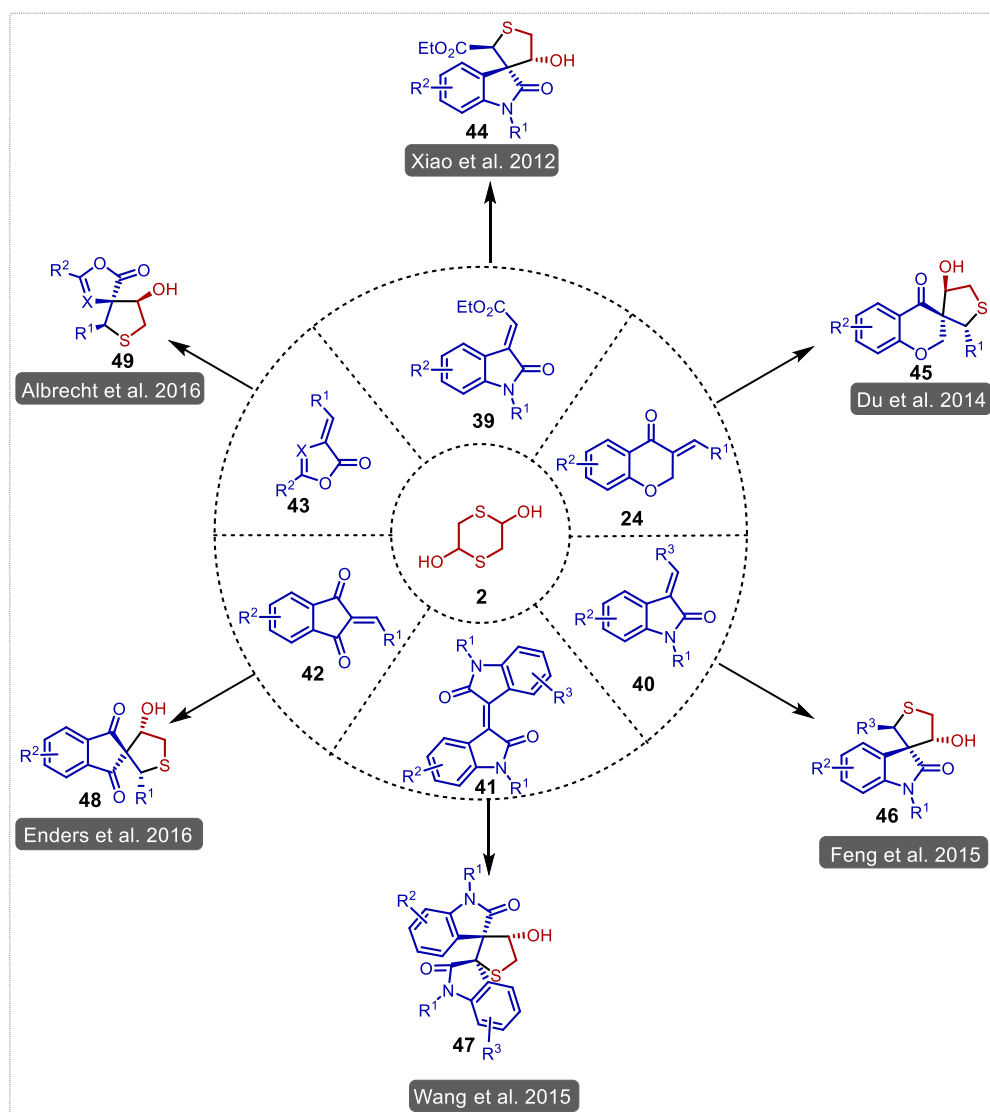
intramolecular aldol reaction instead of 1,6-addition followed by vinylogous Henry reaction. Li's group have shown the construction of spiroindolizine-THTs **36** and spirothiazolotriazine-THTs **37** by applying a similar approach to various activated olefines.⁴⁵ Both the structures and relative stereochemistry of products were confirmed by ¹H-¹³C HMBC correlation and single crystal X-ray analysis. Recently, H. G. Bonacorso has investigated the catalyst-free thia-Michael/aldol reaction of arylidene cycloalkanones **30** with dithiane-diols **2** for the synthesis of bicyclic thiaspiroalkanones **38**.⁴⁶ Notably, the major diastereoisomer is switched by changing the ring size of α,β -unsaturated ketone **30**. In the presence of cyclohexanone derivatives, the major diastereoisomer has a hydroxy group that is *trans* to R¹. However, in the presence of cyclopentanone derivatives, the major diastereoisomer has hydroxy group *cis* to R¹.



Scheme 1.5: Synthesis of spiro-THT derivatives via Michael/aldol reaction of several activated alkenes with 1,4-dithiane-2,5-diol

Several research groups have synthesized enantioenriched spiro-tetrahydrothiophene derivatives by using chiral organocatalyst with the Michael/aldol reaction of 1,4-dithiane-2,5-diol and unsaturated carbonyls (Scheme 1.6). In 2012, Xiao's group have used activated alkenyl-oxindoles **39** as a Michael acceptor to construct spiro-oxindole tetrahydrothiophenes **44** in an asymmetric manner.⁴⁷ Cinchona-derived squaramide catalyst was found to be effective for this thia-Michael/aldol reaction. Another chiral squaramide catalyzed asymmetric cascade thia-Michael/aldol reaction to construct spiro-chromanone THTs **45** was reported by D. M. Du et al.⁴⁸ The developed cascade approach has a wide range of substrate generality, low catalyst loading

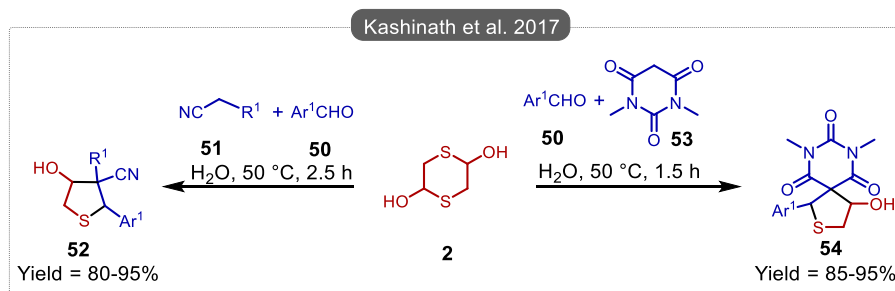
and efficiency to scale-up reaction. In 2015, X. Feng and co-workers have distinguished thia-domino ring-closing reaction of 3-alkenyloxindoles **40** with 1,4-dithiane-2,5-diol.⁴⁹ A library of spirocyclic oxindole-THTs were synthesized in high yield with excellent stereoselectivities. In the same year, a *Cinchona*-alkaloid catalyzed efficient approach has been developed to construct spiro-THTs utilizing isoindigo **41** as a Michael acceptor. In this cascade approach, vicinal quaternary spirocenters bearing chiral bispirooxindole-tetrahydrothiophenes **47** were synthesized in excellent yields and stereoselectivities.⁵⁰ Furthermore, the bispirooxindole-THTs were oxidized to multifunctional products by using selective oxidants like PCC and *m*-CPBA. D. Enders et al. have demonstrated the squaramide-catalyzed thia-Michael/aldol reaction of arylidene-1,3-indandiones **42** with 1,4-dithiane-2,5-diol **2** to access spiro-indane-1,3-dione THTs **48**.⁵¹ In addition, the product was transformed to corresponding carbamate. Furthermore, to determine the relative and absolute configuration of spiro-indanone THTs, single crystal analysis and NOESY experiments were examined. In 2016, Hejmanowska and Albrecht have established an organocatalytic asymmetric strategy to construct butenolide and azlactone motifs holding spiro THTs **49**.⁵²



Scheme 1.6: Asymmetric synthesis of multi-substituted spiro-THTs via Michael/aldol reaction

In 2017, Kashinath and co-workers have reported a one-pot cascade synthesis of highly functionalized THTs featuring a geminal electron-withdrawing group with quaternary centers (Scheme 1.7). The desired THTs **52** and **54** were obtained with the reaction between in-situ generated Knoevenagel condensation product and 1,4-dithiane-2,5-diol **2** under catalyst-free

conditions in water as a solvent.⁵³ They have proposed that the hydrophobic interactions between the insoluble starting materials and the hydrogen-bonded water network are the cause for the aggregation of the starting materials. These non-covalent interactions aid in the association of reactive partners to produce the Knoevenagel condensation product, which will undergo sulfa-Michael followed by intramolecular aldol reactions to afford spiro-THTs.

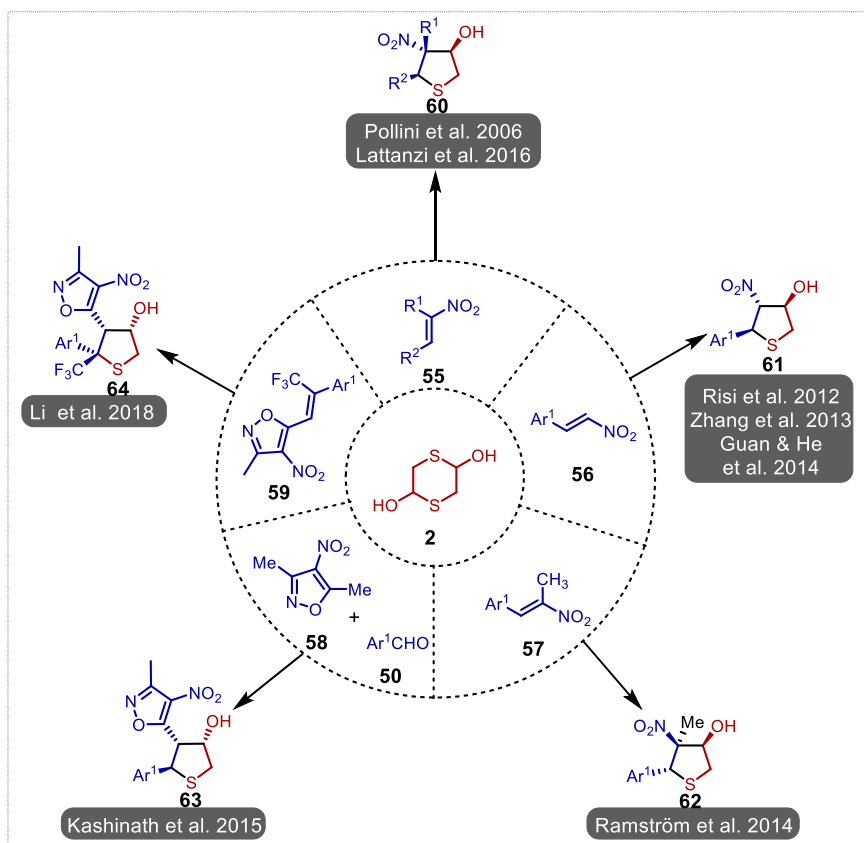


Scheme 1.7: Synthesis of substituted THTs via thia-Michael/aldol reaction of Knoevenagel condensation product

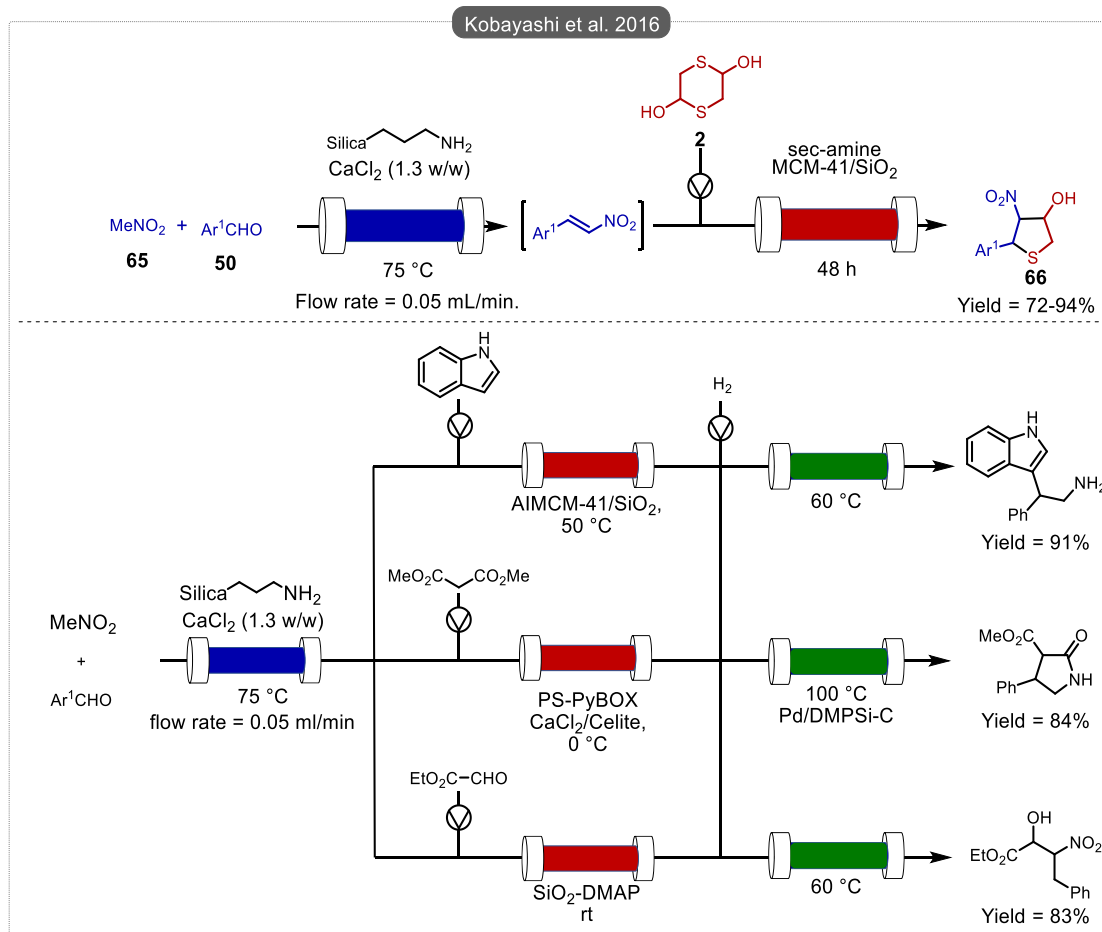
1.1.2 Michael/Henry Reactions

Michael/Henry reaction also known as Michael/nitro-aldol reaction, specifically refers to Michael addition followed by nitro aldol process. It involves the 1,4-addition followed by an intramolecular cyclization between nitro-alkenes and sulfur-containing nucleophiles. Numerous THTs scaffold-containing molecules were synthesized via the Michael/Henry reaction of mercaptoacetaldehyde with nitro olefines (Scheme 1.8).

In, 2006, Pollini and co-workers developed a tandem Michael/Henry reaction of mercaptoacetaldehyde **2** and β -nitroacetates **55**. In-situ generated electrophilic alkenes from β -nitroacetates react with 1,4-dithiane-2,5-diol leading to THTs in good yield.⁵⁴ Zhang's group reported immobilized tertiary-amine catalyzed Michael/Henry reaction of nitrostyrene's **56** and 1,4-dithiane-2,5-diol in 2013.⁵⁵ Further, the fiber catalyst was recycled and reused up to ten cycles. The desired product was obtained with a slight loss of catalytic activity. In addition, DFT calculations were examined to optimize the geometry of products and their energies. It was found that the nitro group is in *trans*-position to both the aryl and the hydroxy group have minimum energy. In 2014, Ramström's group developed a domino thia-Michael-Henry reaction-based dynamic systemic asymmetric transformation process. Lewis's acid and base activation were used in conjunction with the double reversible covalent method to effectively create dynamic systems of compounds with multiple stereogenic centers.⁵⁶ The selection of the main product with high enantiomeric purity was made feasible by further linking the dynamic systems, promptly in situ, to a subsequent kinetically controlled enzymatic resolution step. Kashinath et al. designed a one-pot Knoevenagel condensation/thia-1,6-Michael/intramolecular vinylogous Henry reaction for the synthesis of highly functionalized isoxazole-tetrahydrothiophene **63** derivatives in 2015.⁵⁷ The reaction has proceeded efficiently in the presence of piperidine base with ethanol as a solvent. Lattanzi's group has developed an asymmetric synthesis of quaternary stereocenter holding 3,4,5-substituted THTs. The cascade thia-Michael/Henry reaction of (*E*)-1-aryl-2-nitropropenes **55** with 1,4-dithiane-2,5-diol afforded THTs in high yields with moderate enantioselectivities.⁵⁸ In 2018, Li's group has described DABCO catalyzed 1,6-thia-Michael/Henry reaction of trifluoromethyl-substituted styrylisoxazoles **59** with mercaptoacetaldehyde for the synthesis of the quaternary center bearing trifluoromethyl-substituted THTs **64**.⁵⁹ Based on LC-MS analysis, they have proposed that DABCO activates the nucleophile, mercaptoacetaldehyde, which will undergo 1,6-conjugate addition followed by intramolecular vinylogous Henry reactions to afford the tri-substituted THTs and regenerate the DABCO catalyst.



Scheme 1.8: Synthesis of numerous heterocyclic scaffolds containing THTs via Michael/Henry reaction



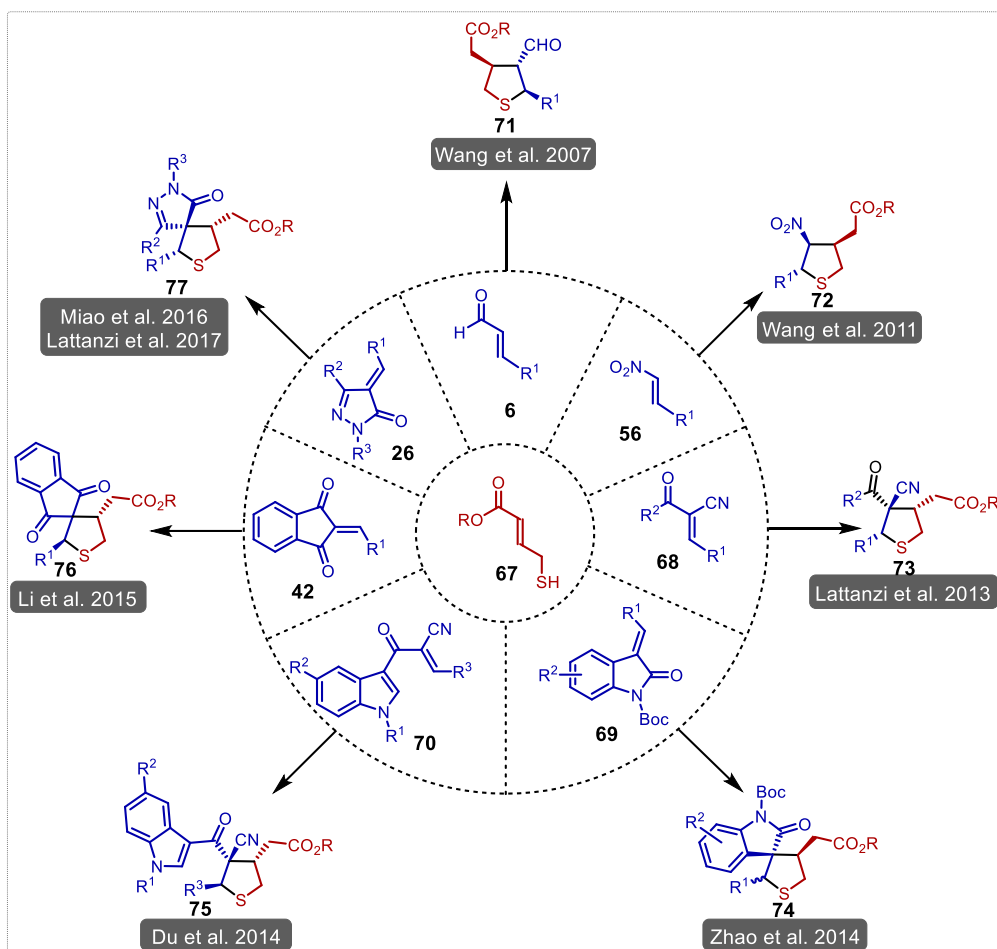
Scheme 1.9: Synthesis of trisubstituted THTs through Michael/Henry reaction under flow-condition

Kobayashi and co-workers have established an eco-friendly and sustainable approach for the synthesis of trisubstituted THTs using continuous flow conditions in the Michael-Henry reaction.⁶⁰ First, they have synthesized β -nitrostyrene derivatives by using an amino-functionalized silica gel catalyst. Next, the column was packed with secondary amine-functionalized, aluminum-containing MCM-41 to catalyze the Michael/Henry reaction. The desired THTs **66** were obtained in 72-94% yield. Furthermore, they have synthesized seven kinds of nitro-group bearing organic compounds via two steps continuous flow systems. In addition, they have successfully conducted three continuous transformations via successive three-step flow reactions in the presence of a heterogeneous catalyst (Scheme 1.9).

1.1.3 Michael-Michael Reactions

The thia-Michael/Michael reactions between mercapto-butenolate analogues and activated olefins are the most efficient and straightforward methods for constructing chiral as well as racemic tetrahydrothiophenes. Several approaches have been developed via utilizing various electrophilic alkenes with sulfur nucleophiles in the presence of a variety of organocatalysts and bases.

In a flurry of papers published in the past few years, almost all of these reports used 4-mercaptopent-2-enolates **67** derivatives as a sulfa-partner for double Michael reaction with α,β -unsaturated carbonyl and nitro compounds to construct several THT scaffolds anchored with diverse skeletons (Scheme 1.10). In 2007, Wang's group developed an efficient organocatalyzed asymmetric Michael-Michael reaction of activated carbonyls **6** with 4-mercaptopent-2-enolate **67**. The reaction was catalyzed efficiently in the presence of (*S*)-diphenylprolinol TMS ether to afford highly functionalized chiral THTs.⁶¹ In addition, it was observed that the reaction of *trans*- α,β -unsaturated aldehydes and ethyl-*trans*-3-(2-mercaptophenyl)-2-propenoate in the presence of the same catalyst with benzoic acid additive led to a single-Michael adduct instead of double-Michael product. In 2011, they reported a bifunctional amine-thiourea-catalyzed double Michael reaction using nitrostyrene **56** as an electrophilic partner with 4-mercaptopent-2-enolates. The reaction was carried out at a low temperature in the presence of Takemoto catalyst to furnish nitro-substituted THTs **72** in good yields with high stereoselectivities.⁶² This cascade approach provides a successful path for the formation of three stereogenic centers, one C-S bond, and one C-C bond. More importantly, a novel activation mode with dynamic kinetic resolution and cooperative direct stereocontrol is discovered. It is demonstrated that to control the stereoselectivity of this cascade approach chiral amine thiourea catalyst played an essential role. Lattanzi et al. showed an efficient asymmetric synthesis of quaternary stereocenter containing THTs via double Michael reaction of α -cyano- α,β -unsaturated ketones **68** with 4-mercaptopent-2-enolates.⁶³ The cascade reaction involves a DKR process which is highly efficient. In addition, they have also developed a one-pot Knoevenagel condensation/double Michael cascade process for the synthesis of tetrahydrothiophenes in high stereoselectivity. Another bifunctional thiourea-catalyzed double Michael reaction was reported by Zhao's group to constructing spirooxindole-THT **74** motifs.⁶⁴ Moreover, they have also developed amino acid-derived thiourea-catalyzed oxa-Michael/Michael cascade synthesis for the synthesis of spiro oxindole-chroman. In 2014, Du and co-workers have synthesized chiral 3-indole substituted THTs **75** utilizing a *Cinchona*-derived squaramide catalyst.⁶⁵ Notably, the R³ group having aliphatic and heteroaryl groups did not provide desired THTs under optimized conditions. Li's group has developed the thiourea-amine catalyzed asymmetric synthesis of spiro-1,3-indanedione-THTs **76** from thia-Michael/Michael reaction of 2-arylidene-1,3-indanediones **42** and 4-mercaptopent-2-enolates.⁶⁶ Furthermore, they have also developed one-pot aldol condensation followed by double-Michael reactions to construct highly functionalized chiral spiro-THTs in significant yield and stereoselectivity. In 2016, Z. Miao et al. reported DABCO-catalyzed diastereoselective synthesis of spiro-pyrazolone tetrahydrothiophenes **77**.⁶⁷



Scheme 1.10: Synthesis of multi-substituted THTs bearing various heterocyclic scaffold through double Michael reaction

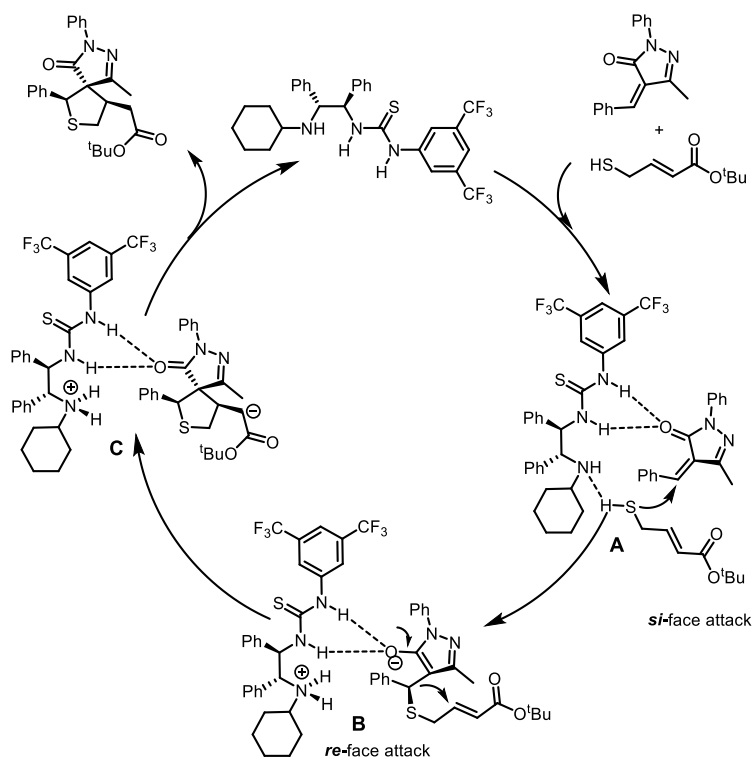
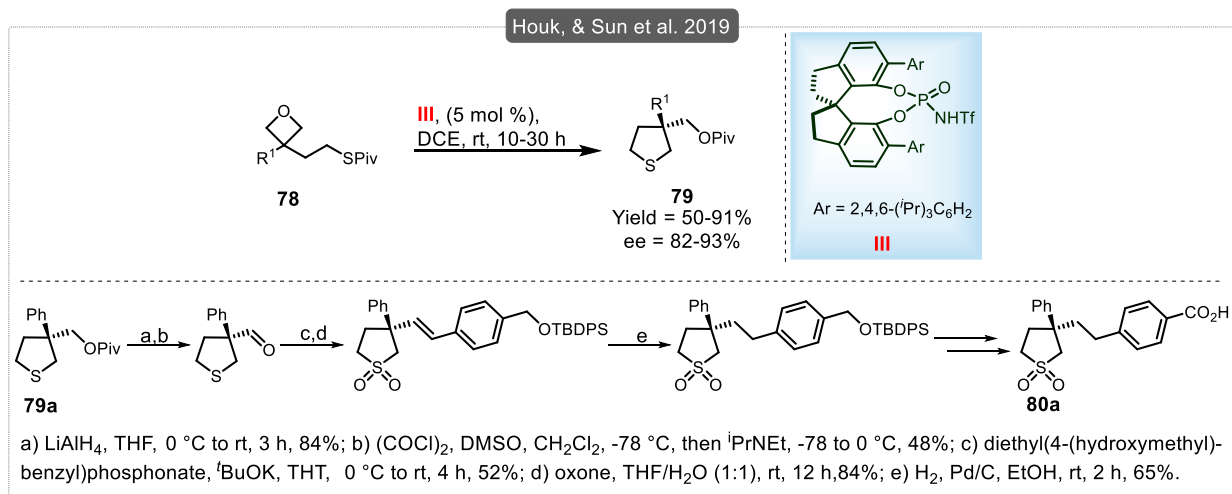


Figure 1.4: Catalytic cycle for bifunctional amine catalyzed double-Michael addition reaction

Next year, Lattanzi's group have developed the asymmetric version of a previously reported work by Miao et al.⁶⁸ The cascade reaction was catalyzed by a (*R,R*)-1,2-diphenylethylenediamine thiourea to furnish desired spiro THTs in high yields and stereoselectivities.⁶⁸ The catalytic cycle for this cascade approach is shown in Figure 1.4. The bifunctional amine activates the pronucleophile **67** and hold the α,β unsaturated pyrazolone **26** via hydrogen bonding. The thiol nucleophile will attack to the Michael acceptor (*Si*-face) to give (*S*)-configured adduct **B**. The enolate of adduct **B** will attack from the *Re*-face to the β -position of ester to afford spiro-THTs in an asymmetric fashion.

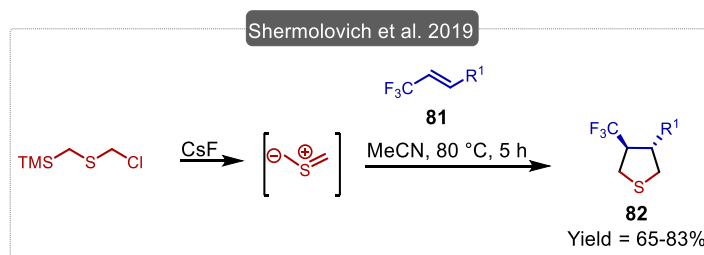
1.1.4 Miscellaneous Reactions

In this part, we have discussed various organocatalyzed desymmetrization and annulation reactions for the synthesis of tetrahydrothiophenes. Houk and Sun's group reported a chiral Brønsted acid-catalyzed oxetanes desymmetrization reaction for synthesizing chiral THTs **79** (Scheme 1.11).⁶⁹ Additionally, in the absence of C2 chirality, this protocol provided a path for creating remote stereocenters at the 3-position. To investigate the mechanism and the origins of stereoselectivity, DFT simulations were performed. It was observed that the orientation of the R¹ group in the substrates in relation to the isopropyl group in the catalyst is the main determinant of selectivity. Furthermore, the products were transformed into the precursor of the bioactive compound thromboxane receptor antagonist **80a**. In addition, the method was further extended to construct tetrahydropyrans.



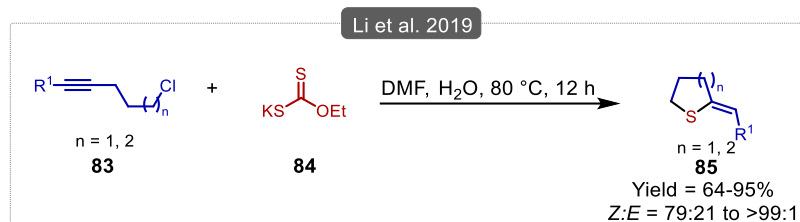
Scheme 1.11: Synthesis of THTs through asymmetric desymmetrization of oxetanes

In 2019, trifluoromethyl substituted THTs were synthesized through [3+2] cycloaddition reaction of in-situ generated thiocarbonyl ylides with 3,3,3-trifluoropropene derivatives **81**.⁷⁰ The synthesized THTs have several substituted groups (ester, sulfone, sulfoximine, sulfonamide, or phosphonate) at 3-position (Scheme 1.12). Furthermore, the sulfur of product **82** was oxidized to S-oxides, S,S-dioxides and S-Imino-S-oxides.



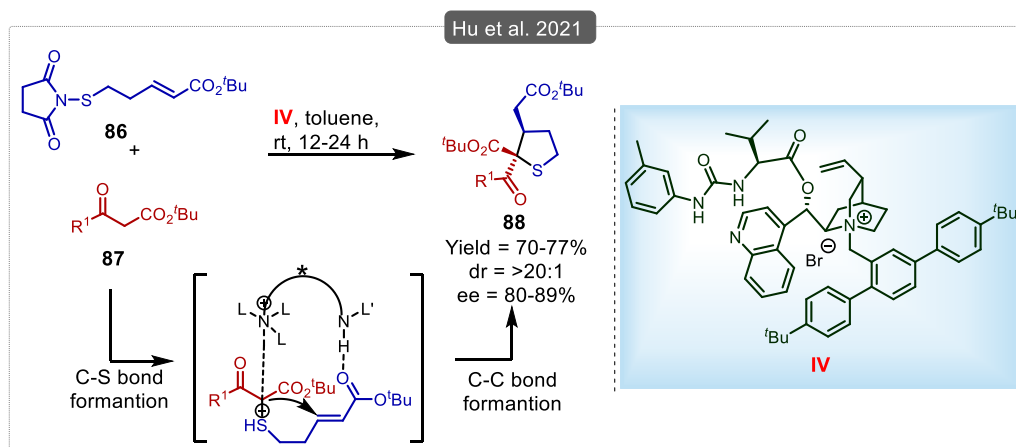
Scheme 1.12: Synthesis of trifluoromethyl-substituted THTs

Li's group developed another novel and efficient cascade approach through nucleophilic substitution followed by intramolecular cycloaddition.⁷¹ They have used EtOCS₂K **84** as a thiol precursor (Scheme 1.13). In this C-S bond-forming reaction, an active intermediate, thionyl radical, is formed in-situ from xanthates. It is the product of the nucleophilic substitution reaction of EtOCS₂K and (5-chloropent-1-yn-1-yl)benzene. In addition, to demonstrate the potential of the developed method, some selective derivatives of **85** were converted into 1,1-dioxide derivatives of tetrahydrothiophenes.

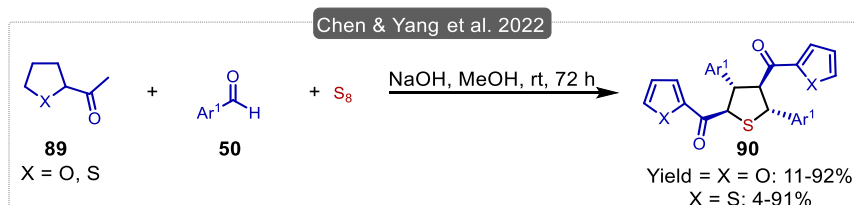


Scheme 1.13: Synthesis of (Z)-tetrahydrothiophenes

Recently, an efficient chiral-PTC catalyzed asymmetric [4+1] annulation reaction to afford consecutive tertiary and quaternary carbon stereocenters containing functionalized 2-acyl-2-carboxyl THTs **88** was reported.⁷² In this new annulation reaction, β -keto esters **87** are used as one-carbon nucleophiles and 5-succinimidothio-pent-2-enoate **86** is used as a four-atom dielectrophilic synthon (Scheme 1.14). This annulation reaction involved the formation of C-S bond via electrophilic sulfenylation reaction and a subsequent formation of the C-C bond via Michael addition reaction of α,β -unsaturated esters. The quaternary nitrogen stabilized the nucleophile and the hydrogen bonding unit of chiral-PTC increases the electrophilicity of β -carbon to facilitate the formation of a new C-C bond. Furthermore, the product **88** may easily undergo two phases of debenzoylation and alkylation processes to provide the chiral 2-alkyl-2-carboxyl tetrahydrothiophenes.



Scheme 1.14: Synthesis of chiral 2,2-disubstituted tetrahydrothiophenes



Scheme 1.15: Synthesis of S-heterocycles via domino reactions

Very recently, Chen and Yang's group have reported a stepwise aldol/double Michael addition/internal S_N2 reaction to construct THTs.⁷³ In this strategy, they have used sulfur powder as a sulfur source with other reactants i.e, 2-acetylfuran/2-acetylthiophene **89**, benzaldehydes **50**. The developed method allows to make a tetrahydrothiophene ring **90**. Importantly, this method allows the construction of five new bonds in one pot (Scheme 1.15).

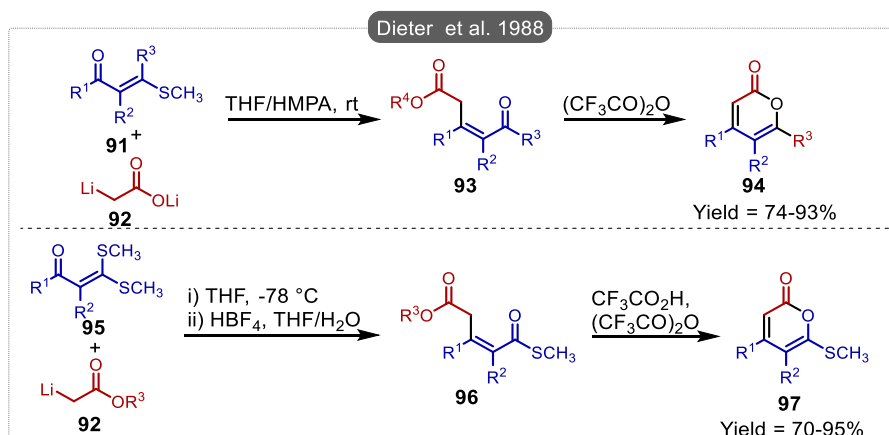
1.2 BRIEF LITERATURE REVIEW FOR THE SYNTHESIS OF α -PYRONES

Oxygen-containing compounds have significant biological and pharmaceutical properties.⁷⁴ α -Pyrones or 2-pyrones are a class of versatile compounds that have exceedingly common structural motifs in a variety of naturally occurring and synthetically produced bioactive compounds with a wide range of chemotherapeutic potentials.⁷⁵ These compounds are characterized by a six-membered one oxygen atom-bearing cyclic structure with a carbonyl group at the α -position. The synthesis of α -pyrones has been extensively investigated, and various efficient methods have been developed to access these valuable compounds.⁷⁶ These synthetic routes offer flexibility in terms of substrate choice and allow for the incorporation of diverse functional groups and substituents. Besides their synthesis, they can also be obtained through natural product isolation and semisynthesis.⁷⁷ Many microorganisms and plants produce α -pyrones as secondary metabolites, which can be isolated and purified from natural sources.⁷⁸ Herein, we have concise the important reports in synthesizing 2-pyrones with a special emphasis on organocatalyzed approaches along with some other significant reports.

1.2.1 Michael Initiated Ring Closing Reactions

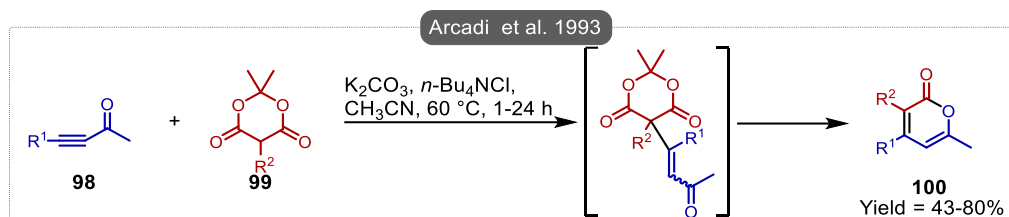
The Michael Initiated Ring Closure (MIRC) reactions⁷⁹ are one of the elegant approaches for the synthesis of oxygen-containing heterocycles especially α -pyrones compounds.⁷⁷ One-pot multicomponent reactions, which are currently significant interest of synthetic organic chemists, can also be used to achieve the MIRC reaction strategy in a creative way. Multi-component reactions (MCRs), which often take place in a single pot and have excellent atom-economy and selectivity, are significant in modern synthetic organic chemistry. Herein, we have abridged some interesting MIRC reactions for the synthesis of 2-pyrones. Initially, the MIRC reaction undergo Michael addition followed by mostly intramolecular cyclization or substitution to afford desired products.

In 1988, Dieter and Fishpagh reported the synthesis of 2-pyrones from α -oxo ketene dithioacetals **95** and vinylogous thiol esters **91** (Scheme 1.16). Products **94** and **97** were formed through multistep reactions involving nucleophilic addition, acid-promoted rearrangement, and enol lactonization. These multistep reactions allowed to access α -pyrones in good yields without isolating and purifying intermediates.⁸⁰



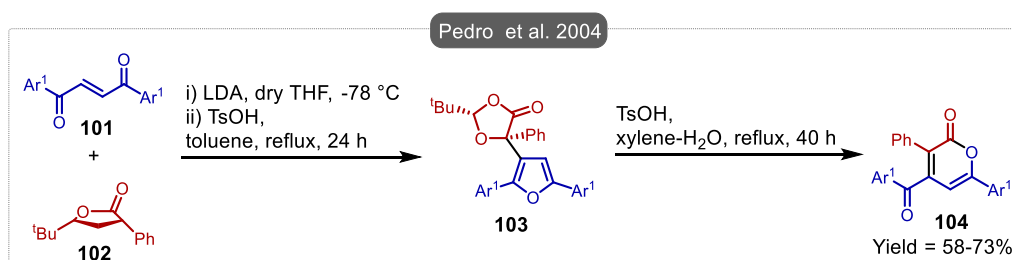
Scheme 1.16: Synthesis of α -pyrones from α -oxo ketene dithioacetals and vinylogous thiol esters

Arcadi synthesized α -pyrones with the reaction of 5-monoalkyl derivatives of Meldrum's acid **99** and α,β -ynones **98** (Scheme 1.17). The reaction was catalyzed by potassium carbonate in the presence of tetrabutylammonium chloride.⁸¹



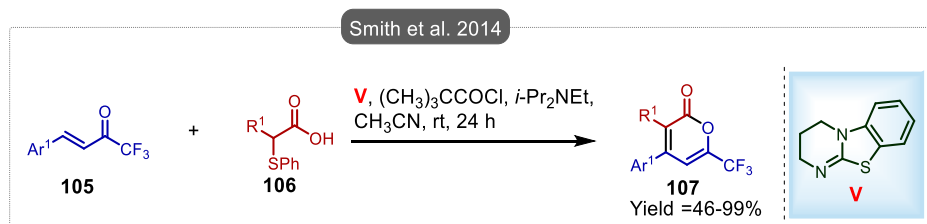
Scheme 1.17: Synthesis of α -pyrones from Meldrum's acid and α,β -ynones

In 2004, Pedro and co-workers envisioned a three-step synthesis of substituted α -pyrones (Scheme 1.18). This one-pot multi-step reaction involved Michael addition of mandelic acid dioxolanone enolate **102** to *trans*-1,2-diaroyl ethenes **101**, acid-mediated cyclization to a furan **103** and lactonization process.⁸²



Scheme 1.18: One-pot reaction of mandelic acid enolate and *trans*-1,2-diaroyl ethenes

Smith and co-workers have established a one-pot isothiurea-mediated (V) cascade reaction of α,β -unsaturated trifluoromethyl ketones **105** and (phenylthio)acetic acids **106**. This Michael addition/lactonization/thiol elimination cascade sequence allowed to construct disubstituted and trisubstituted 2-pyrones **107** in high yield (Scheme 1.19). Initially, (phenylthio)acetic acids **106** react with the acyl chloride to form an ester and then react with isothiurea to generate intermediate **A**. In the presence of a base, it will form enolate and undergo Michael addition followed by lactonization to create dihydropyrene **B** and regenerate the catalyst. Afterward, dihydropyrene **B** will undergo E1cB elimination to afford α -pyrones **107** (Figure 1.5). Further, the products were also transformed into trifluoromethyl substituted aromatic and hetero-aromatic compounds.⁸³



Scheme 1.19: One-pot isothiurea-mediated synthesis of 2-pyrones

Several research groups have developed various synthetic routes to α -pyrones via utilizing α -halo esters **108** as a synthon (Scheme 1.20). Ma and co-workers have developed Michael addition/lactonization reaction of EWG substituted acetates **108** with 1,2-allenyl ketones **109** in 2002. The reaction was catalyzed by K_2CO_3 to afford α -pyrones in high yield.⁸⁴ Next year, they have reported K_2CO_3 catalyzed synthesis of β,γ -unsaturated ketones from the reaction of substituted 1,2-allenic ketones with diethyl malonate. Further, extended to the synthesis of α -

pyrones. The product α -pyrones **112** were formed via sequential Michael addition, C-C double bond migration, and lactonization steps.⁸⁵

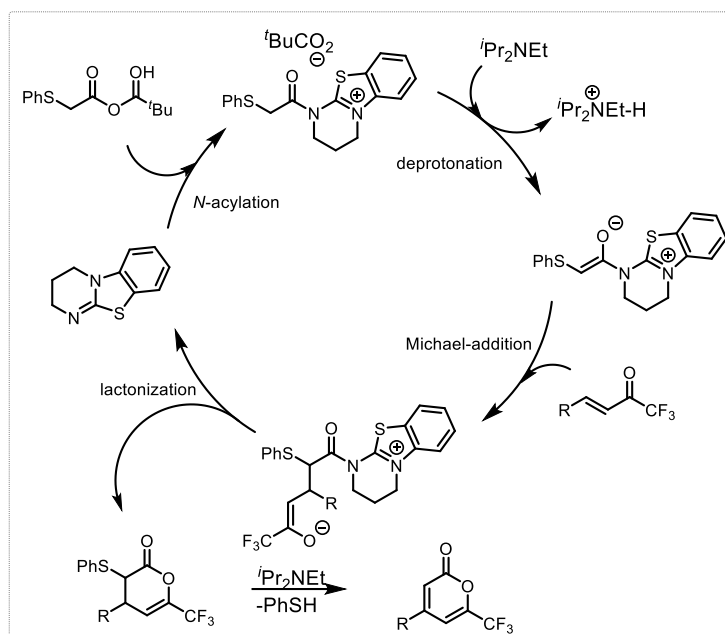
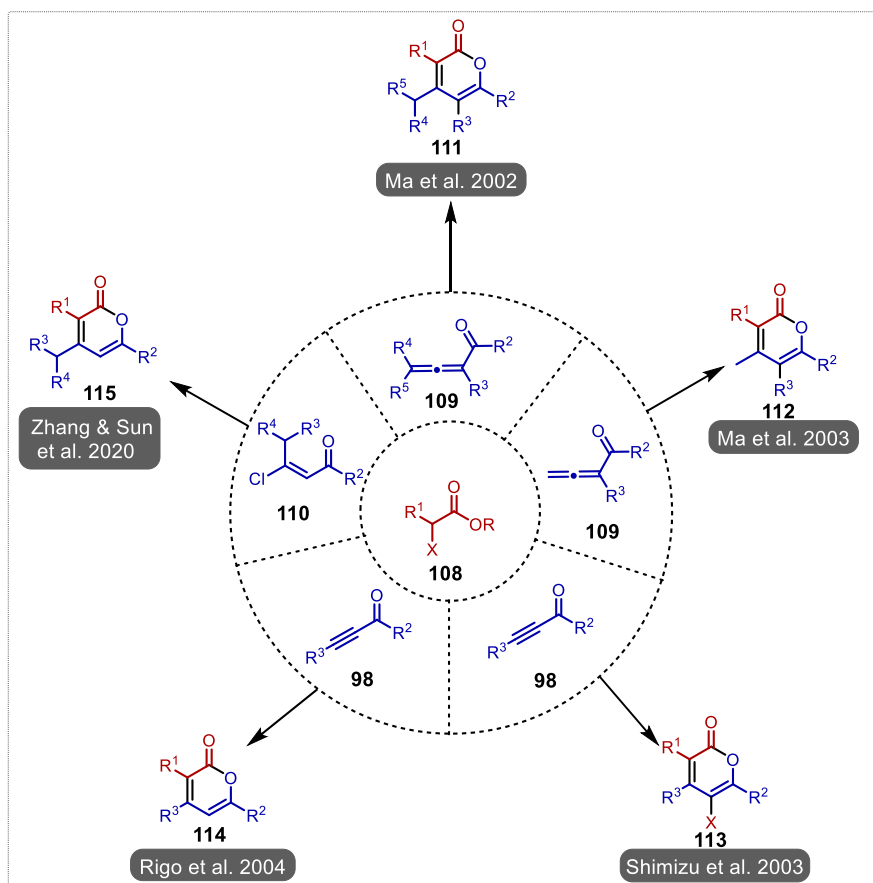


Figure 1.5: Catalytic cycle for isothiurea catalyzed cascade synthesis of 2-pyrones

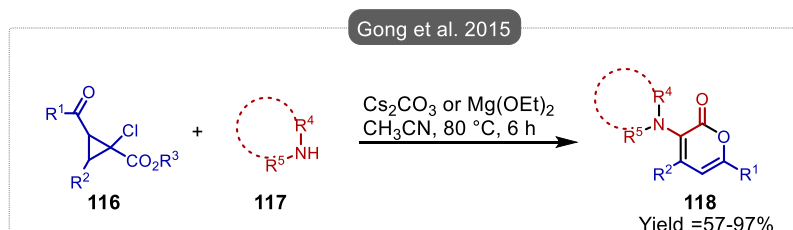


Scheme 1.20: Michael initiated ring closing reactions of several substituted unsaturated carbonyls

In 2003, Shimizu and co-workers established an efficient Michael addition/lactonization reaction of active methine group containing compounds to 2-alkynone **98**.⁸⁶ Next year, Rigo's group have demonstrated the Michael addition/lactonization reaction of acetylenic dicarboxaldehyde monoacetal with substituted Meldrum's acid resulting the formation of

carboxaldehyde substituted α -pyrones.⁸⁷ Further, this carboxaldehyde group was reduced to corresponding alcohol by using NaBH₄. In 2020, Zhang and Sun's group have established the Michael addition/lactonization approach of for the synthesis of α -pyrones from several active methylene-containing compounds and β -chlorovinyl ketones **110** in the presence of potassium carbonate.⁸⁸ Moreover, to highlight the significance of [3+3] cyclocondensation, they have established an efficient protocol for the synthesis of benzofuran derivative and penta- or hexa-substituted phenols by using β -chlorovinyl ketones.

In 2015, Zhu and Gong have reported an inorganic base-mediated domino sequence between amines **117** and 2-acyl-1-chlorocyclopropaneformic esters **116** (Scheme 1.21). In this metal-free domino reaction sequence, substrates were undergo 1,2-elimination/aza-Michael addition/ring-opening followed by a lactonization step to afford α -pyrones **118** (Figure 1.6).⁸⁹ Initially, in the presence of base, **116** undergo simple 1,2-elimination to produce the extremely reactive intermediate cyclopropene **A**. Then nucleophilic amine will react with **A** via aza-Michael addition to generate new cyclopropane intermediate **B** having donor-acceptor groups (D-A). This kind of cyclopropane **B** would quickly convert into an unstable iminium intermediate **C** via a spontaneous ring-opening. Subsequently, deprotonation and intramolecular lactonization led to 2-pyrone. The iminium **C** would readily undergo common hydrolysis to become 2-ketoester **D** in the presence of water.



Scheme 1.21: Metal-free base-mediated domino sequence between amines and cyclopropane formic esters

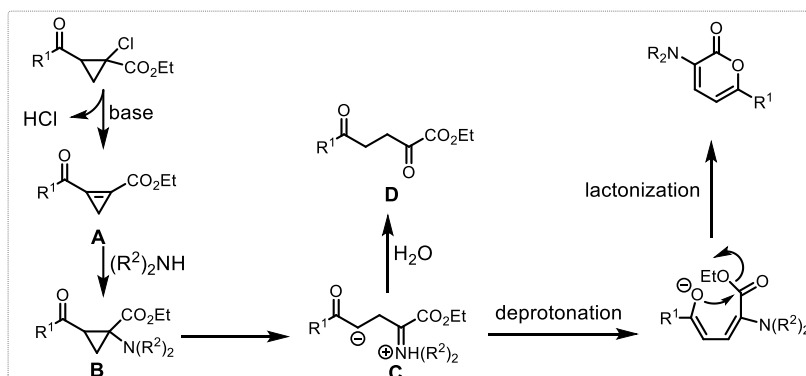
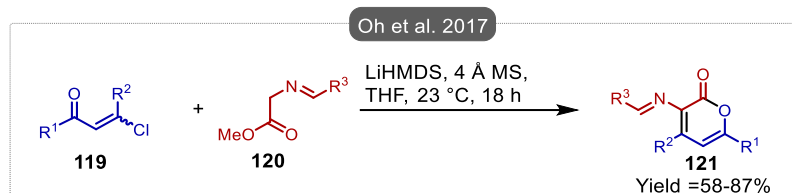


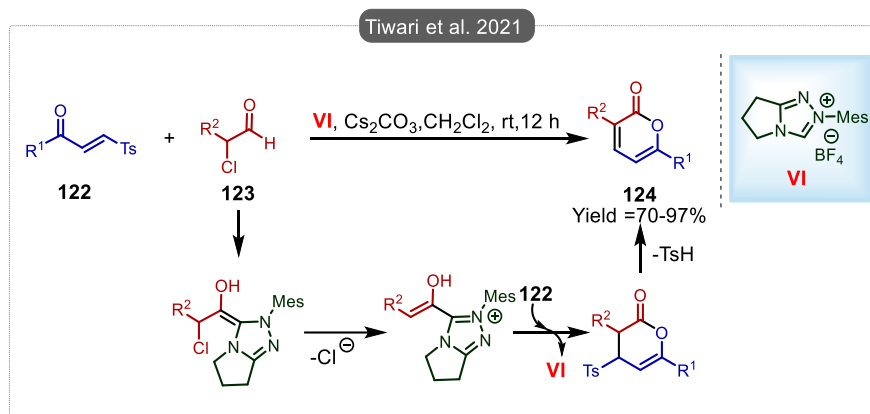
Figure 1.6: Proposed mechanism for the domino synthesis of α -pyrones

An efficient and easy one-pot synthetic process for a variety of heterocycles with the use of selective enolate production from imino esters **120** prompted by the strong base, LiHMDS, was reported by Kim and Oh (Scheme 1.22). This new method highlighted the unique electrophilic nature of β -chlorovinyl ketones **119** and produced conjugate adducts with a basic character – autocatalysis.⁹⁰ By using this innovative approach, they have constructed highly functionalized amine substituted α -pyrone derivatives **121** by using sequential 1,4-addition/elimination/cyclization step followed by either reaction with amines or reduction.



Scheme 1.22: Synthesis of highly functionalized α -pyrone derivatives

In 2021, Tiwari group have envisioned the first NHC (VI) catalyzed Michael addition/elimination/lactonization domino reaction of β -tosyl enones **122** and α -chloro aldehydes **123** for the synthesis of disubstituted α -pyrones (Scheme 1.23). Further, the products were transformed into synthetically viable compounds.⁹¹



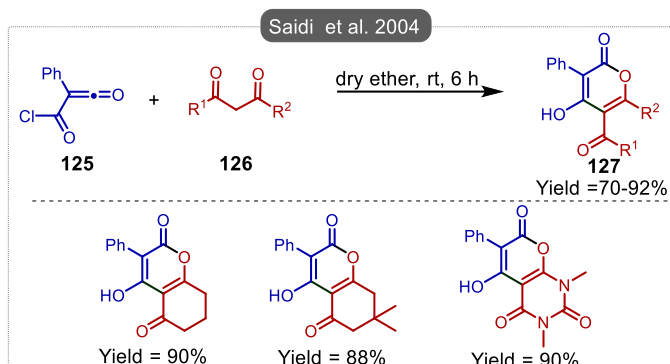
Scheme 1.23: Cascade reaction of β -tosyl enones and α -chloro aldehydes

1.2.2 Annulation Reaction

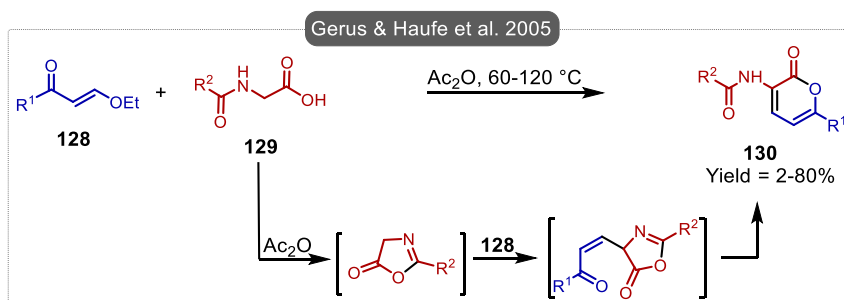
The word "annulation" is derived from the Latin word "*annulus*," which means "ring," and refers to the development of a ring structure during the reaction. Annulation reactions are an effective tool in organic synthesis, allowing for the construction of complex and diverse cyclic structures with significant properties and activities.⁹² They involve the formation of cyclic compounds through the combination of two or more fragments of molecular structures. Several metal- and organo-catalyzed annulation reactions have been demonstrated for constructing α -pyrones.⁹³ Among them, we have discussed selective organo- and base-catalyzed annulation reactions for the synthesis of α -pyrones. Several annulation reactions have been catalyzed by using external oxidants were also discussed here.

In 2004, Saidi and co-workers reported a one-step condensation method for the synthesis of α -pyrones from readily available 1,3-diketones **126** and (chlorocarbonyl)phenyl ketene **125** (Scheme 1.24). The reaction was proceeded without using any catalyst.⁹⁴ Furthermore, the reaction was tested with cyclic 1,3-diketones and pyrimidine-2,4,7-trione to construct 7,8-dihydro-6*H*-chromene-2,5-diones and 1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7,(3*H*)-trione respectively.

In 2005, Gerus and Haufe's group synthesized polyfluoroalkyl-2*H*-pyran-2-ones **130** from the condensation/cyclization reaction of *N*-acylglycines **129** and β -alkoxyvinyl poly-fluoroalkyl ketones **128** (Scheme 1.25).⁹⁵ It was observed that electron-withdrawing substituents such as poly-fluoroalkyl groups strongly activate the carbonyl group of enones **128** and the reaction facilitated in the presence of electron-donating substituents at the benzene ring of hippuric acid.

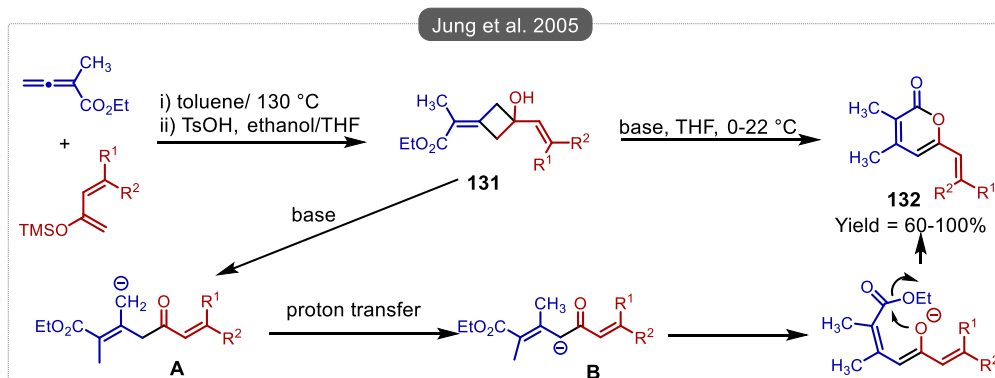


Scheme 1.24: One-pot synthesis of substituted 2-pyrone derivatives



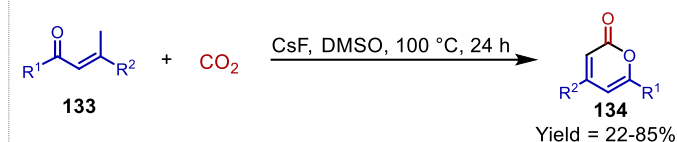
Scheme 1.25: Synthesis of amino-substituted 2-pyraones through condensation/cyclization process

Jung and Novack synthesized 3-carboethoxyethylidene cyclobutanols **131** by [2+2] cycloaddition/acid hydrolysis reaction of allene carboxylate and 2-silyloxydienes (Scheme 1.26).⁹⁶ Further, these cycloaddition products went sequentially ring-opening/proton transfer/isomerization/lactonization steps in the presence of a base to afford 3,4-dimethylsubstituted α -pyrones **132** in high yield. They have proposed that cyclobutanols **131** undergo deprotonation followed by a ring-opening reaction to generate intermediate **A** in the presence of a base. The formation of intermediate **A** is regio-specifically. Therefore, the carbanion is *cis* to the ester. It will undergo proton transfer to generate intermediate **B** that will be stabilized via the allylic ester. Finally, it will undergo lactonization followed by elimination steps led to desired pyrones **132**.



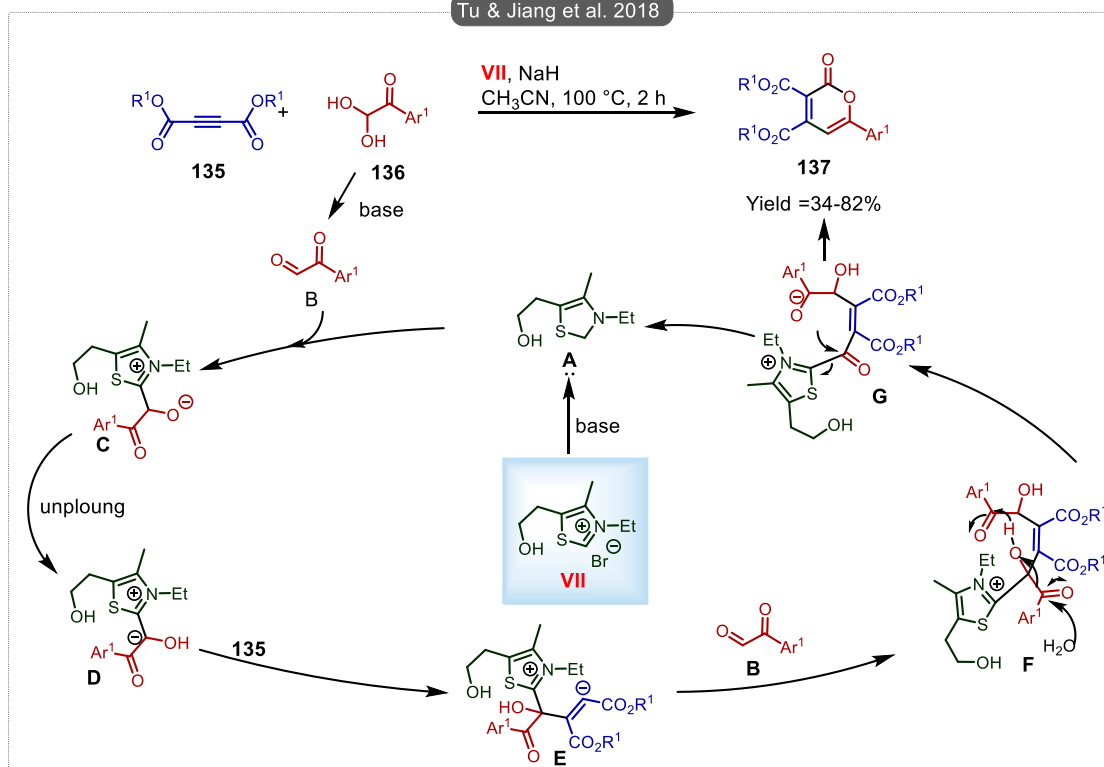
Scheme 1.26: Synthesis of 3,4-dimethylsubstituted α -pyrones

Zhang's group described an effective, transition-metal-free, and simple method for producing significant α -pyrones via carboxylative cyclization of substituted 1-propenyl ketones **133** using carbon dioxide. This γ -carboxylation was promoted by cesium fluoride (Scheme 1.27).⁹⁷ Furthermore, the reaction was performed with ^{18}O -labelled carbondioxide, two ^{18}O -atoms are not detected in MS. It will show that the cyclization takes place via an enolate oxygen atom of **133**.



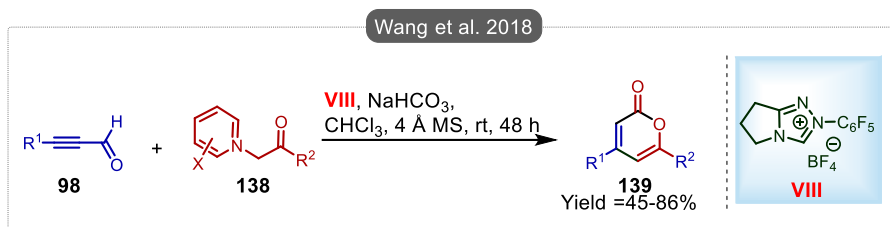
Scheme 1.27: γ -Carboxylation reaction for the synthesis of α -pyrones

In 2018, Tu and Jiang's group devised a novel [3+2+1] annulation reaction of arylglyoxals **136** and acetylene dicarboxylates **135**.⁹⁸ This cyclization reaction was catalyzed by thiazolium salt (**VII**) to afford trisubstituted 2-pyrones (**137**) (Scheme 1.28). In this cyclization reaction, arylglyoxals served as both a source of carbonyls and a component of rings. Initially, in situ generated thiazolium carbene reacted with an in situ formed 2-oxoacetaldehyde from arylglyoxal. This intermediate is converted into a nucleophile via an unploughing process and attacks to **135** to generate another nucleophile that will undergo an aldol-type reaction with another molecule of arylglyoxals followed by proton transfer and elimination to afford α -pyrones **137**.



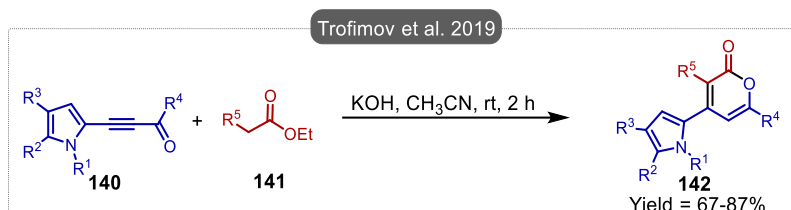
Scheme 1.28: [3+2+1] annulation reaction of arylglyoxals and acetylene-dicarboxylates

Wang and co-workers demonstrated an efficient NHC-catalyzed annulation reaction of pyridinium ylides **138** with ynals **98** (Scheme 1.29).⁹⁹ The reaction goes via simple Michael addition of pyridinium ylides **138** to activated ynals followed by intramolecular cyclization to afford desired α -pyrones efficiently. This protocol had a wide range of substrate and functional group tolerance and afforded α -pyrone derivatives in good to high yield. In addition, the reaction was tested with in situ generation of pyridinium salt. However, a moderate yield was obtained.



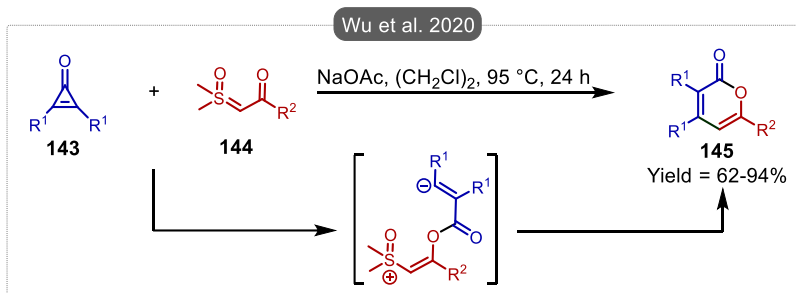
Scheme 1.29: Annulation reaction of ammonium ylides and ynals via NHC-catalysis

In 2019, Trofimov and his group have synthesized a novel class of extended heteroarene (arene-pyrrole-pyrone-arene) conjugated compounds **142** in single step. These highly functionalized pyrrole-pyrone complex molecules were synthesized by [4+2] cycloaddition reaction of acylethynylpyrroles **140** and active methylene esters **141** under mild conditions (Scheme 1.30).¹⁰⁰

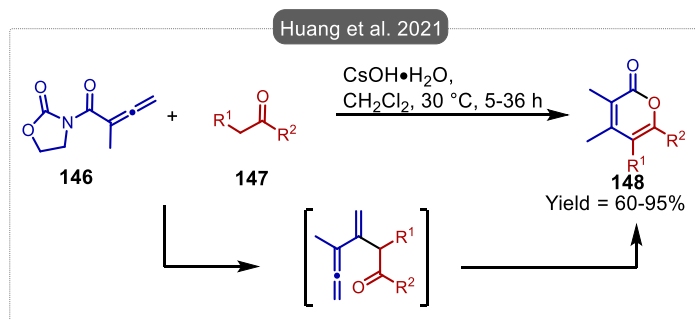


Scheme 1.30: Synthesis of pyrrole-pyrone complex molecules via [4+2] cycloaddition reaction

In 2020, Wu have accomplished an efficient and synthetically valuable tandem synthesis of trisubstituted 2-pyrone derivatives from cyclopropanones **143** and sulfoxonium ylides **144** (Scheme 1.31).¹⁰¹ This [3+3] cycloaddition reaction was conducted under metal-free conditions. A variety of 2-pyrones were produced in moderate to high yields with a broad range of functional groups. In this reaction, nucleophilic addition of enol anion of **144** to the carbonyl group of **143** followed by ring opening to afford intermediate **A**. It will undergo 6-*exo-trig* cyclization led to α -pyrones.



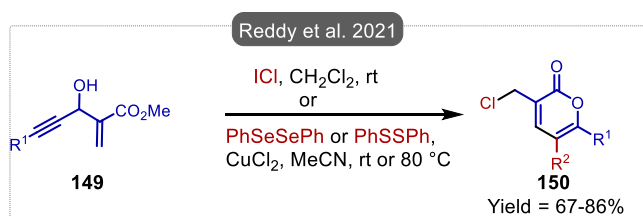
Scheme 1.31: Metal-free cycloaddition reaction of cyclopropanones and sulfoxonium ylides



Scheme 1.32: [3+3] cycloaddition reaction of activated ketones with allenyl imide

Huang's group demonstrated another [3+3] cycloaddition reaction of activated ketones with allenyl imide **146** in 2021.¹⁰² Tetra-substituted 2-pyrone derivatives were synthesized in good yield (Scheme 1.32). In this reaction, the product was formed by the conjugated addition of the carbon anion to allene to form a ketyl intermediate and further cyclization occurs by the removal of the 2-oxazolidinyl group.

Reddy and co-workers have developed base-mediated Iodo- and Chalcogenoannulation reactions of MBH alcohols of propionaldehyde. This intramolecular annulation reaction provides a huge variety of iodine and chalcogen substituted 3-(chloromethyl)-2-pyrones **150** (Scheme 1.33).¹⁰³ The reaction relies on the formation of cyclohalonium ion followed by intramolecular lactonization/elimination/hydrolysis to afford halo-substituted pyrones (Figure 1.7). Further, the chloromethyl group of products was readily transformed into other valuable functionalities.



Scheme 1.33: Annulation reaction of MBH-alcohols of propionaldehydes

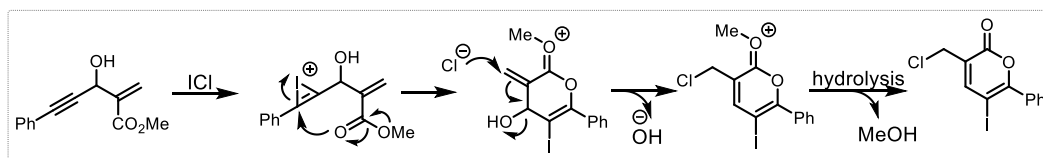
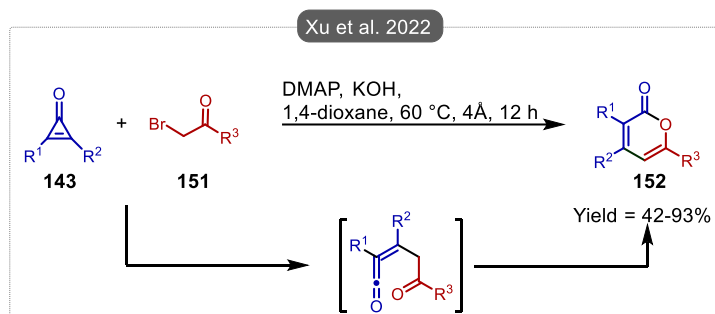


Figure 1.7: Proposed mechanism of Iodo- and Chalcogenoannulation reactions for the synthesis of α -pyrones

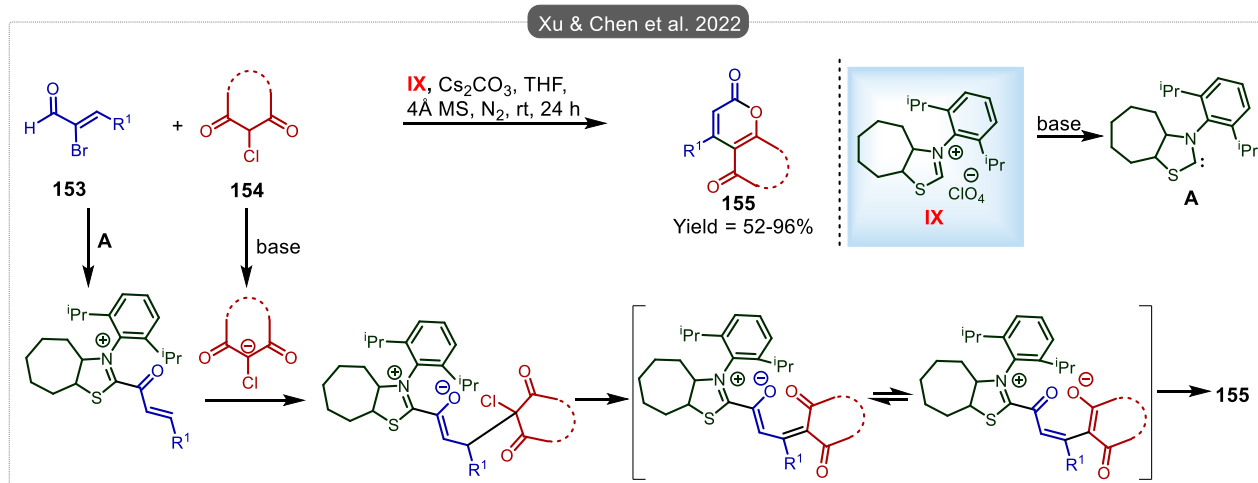
Recently, Xu's group has demonstrated DMAP catalyzed simple and facile approach for the construction reaction of α -pyrones through the [3+3] cycloaddition reaction of α -bromoketones **151** and cyclopropenones **143** (Scheme 1.34).¹⁰⁴ The mechanism of this reaction including pyridinium ylide-initiated cyclopropenone ring opening, elimination of the DMAP catalyst to give ketene intermediate. Finally, it will undergo 6 π -electrocyclization to give α -pyrones. Further, the mechanism was confirmed by experimental analysis and DFT simulations.



Scheme 1.34: DMAP catalyzed [3+3] cycloaddition reaction of α -bromoketones and cyclopropenones

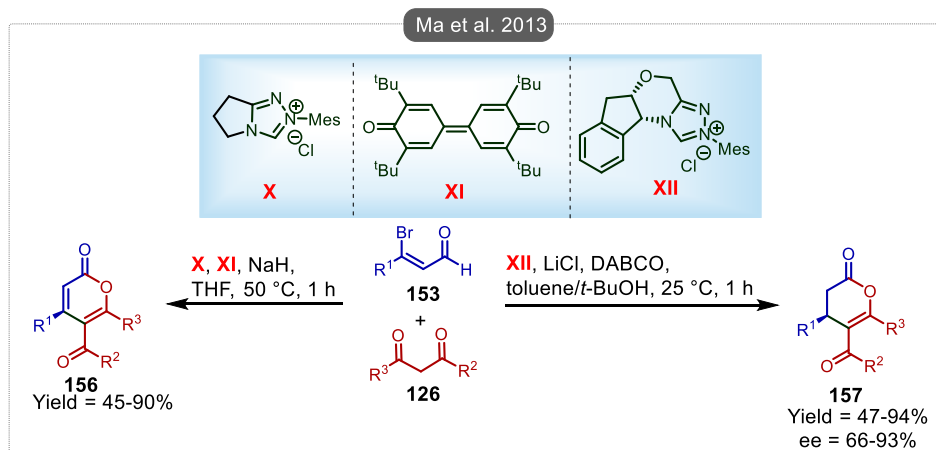
Very recently, Xu and Chen have envisioned NHC-catalyzed oxidant free [3+3] annulation reaction of 2-chloro-1,3-diketones **154** and bromoenals **153** (Scheme 1.35).¹⁰⁵ Trisubstituted α -pyrones with different substituents and substitution patterns were synthesized in good to excellent yields utilizing this protocol. In the presence of base, NHC catalyst is deprotonated and reacts with **153** to generate electrophilic intermediate α,β -unsaturated

acylzolium ion. It will undergo Michael addition with in situ generated nucleophiles followed by lactonization to afford α -pyrones.



Scheme 1.35: NHC-catalyzed oxidant-free [3+3] annulation reaction of diketones and enals

Ma and co-workers have presented oxidative NHC-catalyzed divergent synthesis of 2H-pyran-2-ones **156** and chiral dihydropyranones **157** from 3-bromo-enals **153** and 1,3-dicarbonyls **126** (Scheme 1.36).¹⁰⁶ The divergence of oxidative transformation of 3-bromo-enals under NHC catalysis was controlled by the selective generation of two paths, by an external oxidant or by elimination of reducible β -bromide. A control experiment was conducted to confirm the mechanistic path, i.e.; adding water as a nucleophile instead of **153**. The formation of carboxylic acid derivatives indicated the presence of unsaturated acylzolium ions **B** and **E**. Based on these results, they have proposed the mechanism of this cascade approach (Figure 1.8). Initially, conjugated β -bromo Breslow intermediates **A** and **A'** are formed from the reaction of in situ generated carbene with 3-bromo-enals. In the presence of an external oxidant, it is converted into β -bromo unsaturated acylazoliums **B** and undergo 1,4-addition with deprotonated 1,3-dicarbonyl compounds. Finally, cyclization followed by bromide elimination to produce 2H-pyran-2-ones by releasing a carbene catalyst. Contrarily, proton transfer of homo-enolate **A'** takes place by a weak base in the absence of external oxidants, to afford ester enolates **D**. Next, the removal of bromide to generate azoliums **E**. The catalyst was renewed by Michael addition of 1,3-carbonyl compounds to **E** and then ring closure to produce the annulation product **157**.



Scheme 1.36: NHC-catalyzed divergent synthesis of 2H-pyran-2-ones and chiral dihydropyranones

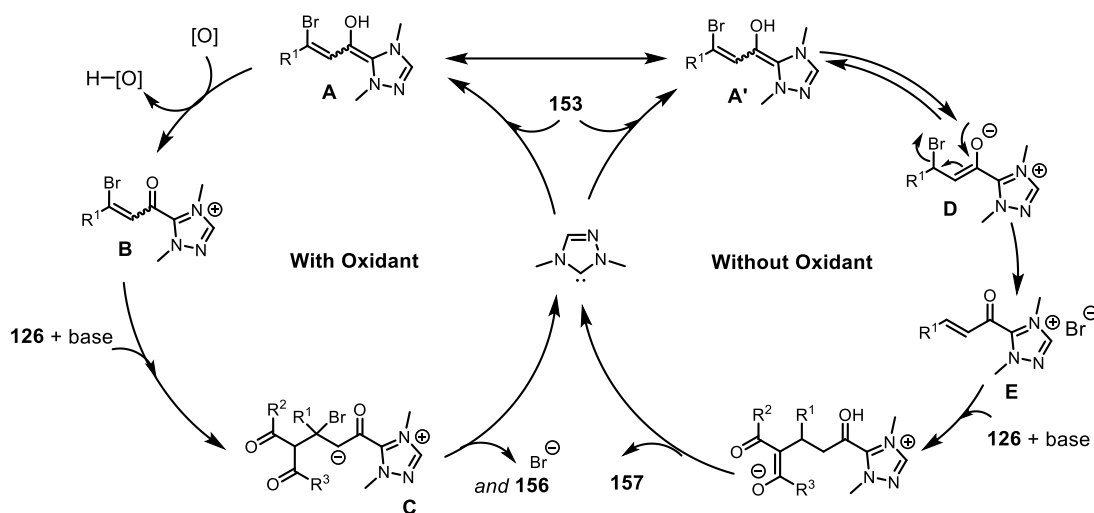
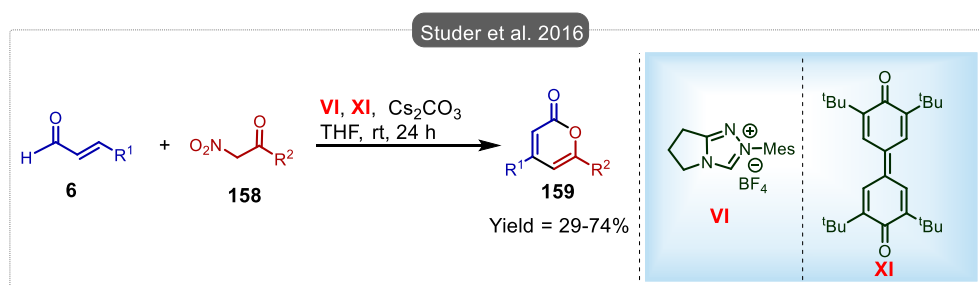


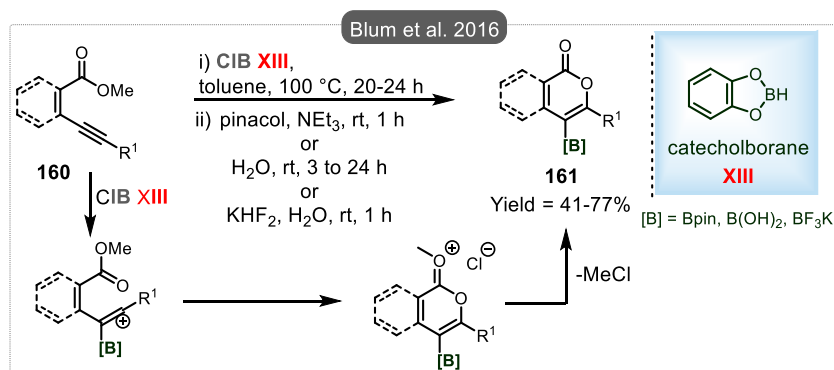
Figure 1.8: Proposed catalytic cycle for NHC-catalyzed cascade synthesis of pyrones

Another oxidative NHC catalysis was developed by Bera and Studer to synthesize 4,6-disubstituted α -pyrones.¹⁰⁷ Nitromethanes **158** and enals **6** with aryl substitutions are used as substrates in this method. The reaction was proceeded via an addition-elimination-lactonization process (Scheme 1.37). The nitro group of α -nitroketone plays two roles during this transformation: stabilizing the enolate and behaving as an anionic leaving group.



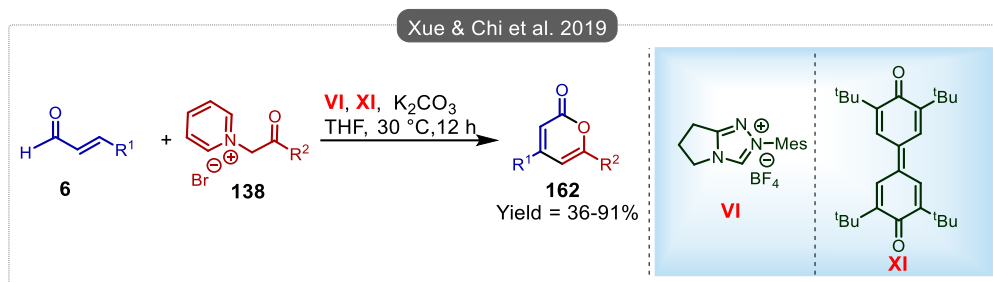
Scheme 1.37: Synthesis of 4,6-disubstituted α -pyrones via oxidative NHC-catalysis

In 2016, Blum's group established a catalyst-free oxyboration reaction of alkynes to access borylated α -pyrones **161** and isocoumarins (Scheme 1.38).¹⁰⁸ Mechanistic investigations showed that the *B*-chlorocatecholborane (**XIII**) behaves as a carbophilic Lewis acid towards alkyne, afforded a mechanistically unique mechanism for oxyboration followed by intramolecular nucleophilic attack of an oxygen atom to vinylic cation to give cyclized oxocarbenium ion. It will undergo rapid dealkylation to afford α -pyrones.



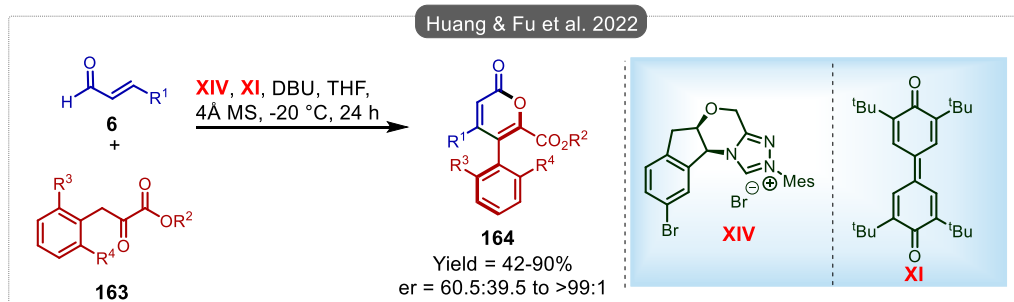
Scheme 1.38: Catalyst-free oxyboration reaction of alkynes

In 2019, Chi et al. also demonstrated the chemistry of ammonium ylide **138** and developed an NHC-catalyzed oxidative [3+3] annulation reaction of nitrogen ylides with enals **6** to access α -pyrones (Scheme 1.39).¹⁰⁹ In these reactions, the 2-pyrone compounds are typically produced in higher yields, and the widely accessible pyridinium salts are used as a precursor of nitrogen ylides. The cascade approach goes via a similar mechanism as shown in Figure 1.8.



Scheme 1.39: NHC-catalyzed oxidative [3+3] annulation reaction of enals with nitrogen ylides

Recently, Huang and Fu have revealed NHC-catalyzed atroposelective synthesis of axially chiral heteroaryl-aryls **164** via highly enantioselective Coates-Claisen rearrangements of in situ formed α,β -unsaturated acyl azoliums with sterically hindered enols **163**.¹¹⁰ In this cascade approach α,β -unsaturated acyl azoliums undergo 1,2-addition followed by Coates-Claisen rearrangements to generate similar type intermediate **C** as shown in Figure 1.8. Further, tautomerization followed by lactonization led to axially chiral 2-pyrones. Furthermore, the axially chiral 2-pyrones were transformed into prevalent biaryl atropisomers through the D-A reaction (Scheme 1.40).

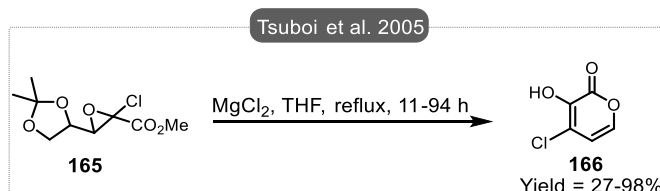


Scheme 1.40: NHC catalyzed atroposelective synthesis of axially chiral α -pyrones

1.2.3 Miscellaneous Reactions

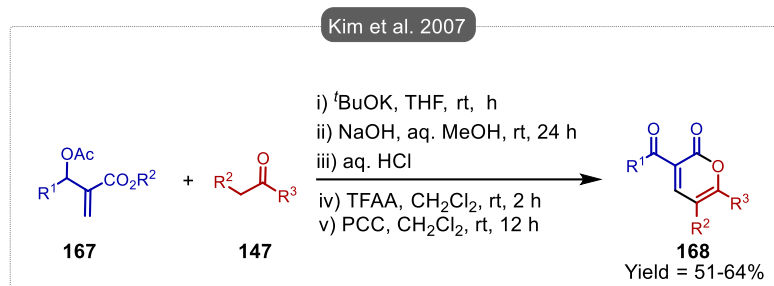
Apart from the above-mentioned categories, selective metal-free approaches for constructing α -pyrones efficiently were summarized in this section.

Tsuboi and co-workers established an innovative one-pot rearrangement-cyclization reaction of acetonide-protected 4,5-dihydroxy-2-chloroglycidic ester **165** with MgCl_2 to afford 4-halo-3-hydroxy-2-pyrone **166** (Scheme 1.41).¹¹¹ In this one-pot reaction, glycidic acid **165** is converted into ketoester in the presence of magnesium chloride. Then the elimination of acetone via keto-enol tautomerism, subsequently intramolecular lactonization followed by keto-enol tautomerism, led to 4-halo-3-hydroxy-2-pyrones.



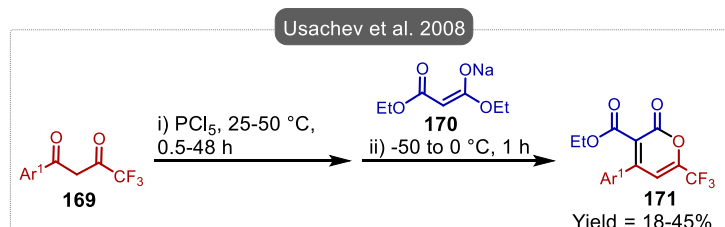
Scheme 1.41: One pot rearrangement–cyclization reaction for synthesizing of 4-halo-3-hydroxy-2-pyrone

Kim used Baylis-Hillman adducts as a starting material for the synthesis of 3,5,6-trisubstituted α -pyrones **168**. Initially, a ketone was added to the Baylis-Hillman adduct, then lactonization followed by PCC oxidation to afford α -pyrone derivatives (Scheme 1.42).¹¹²



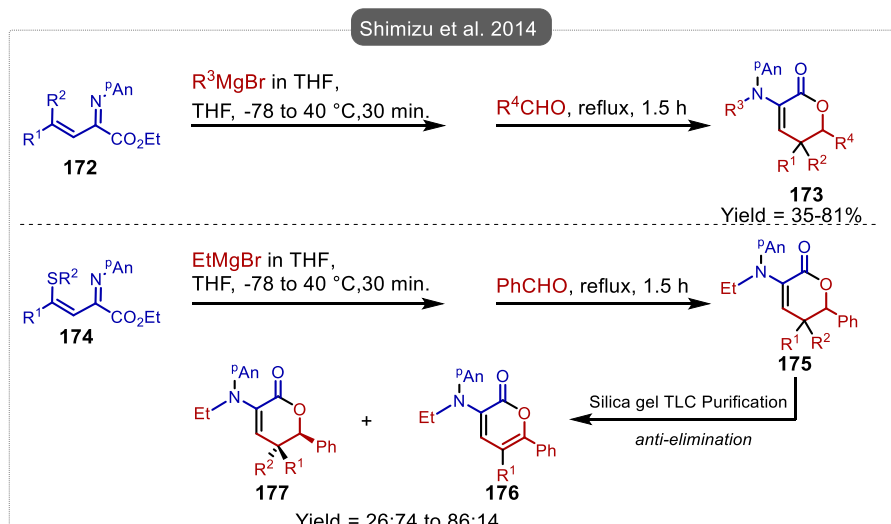
Scheme 1.42: Synthesis of substituted 2-pyrones from BHA

Usachev developed another approach for synthesizing trifluoromethyl substituted 2-pyrones **171** from the reaction of 4,4,4-trifluorobutane-1,3-diones **169** and phosphorus pentachloride in the presence of sodium diethyl malonate **170** at low temperature (Scheme 1.43).¹¹³ Furthermore, the products were transformed into synthetically valuable compounds.



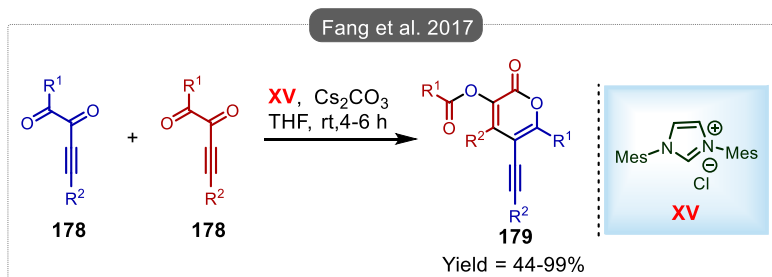
Scheme 1.43: Synthesis of a series of CF_3 group containing 2-pyrones

In 2014, Shimizu's group devised the *N*-alkylation/vinylogous aldol tandem reaction of β,γ -alkenyl α -iminoesters **172**. It was found that the sulfonyl substituents **174** on the alkene portion of the substrates significantly improved the selectivities of both stages and stimulated the production of 3-amino pyrones via anti-elimination (Scheme 1.44).¹¹⁴ The cascade reaction relies on *N*-alkylation followed by an aldol reaction with dienolate via γ -addition. Then intramolecular lactonization to afford amino-substituted 2-pyrones.



Scheme 1.44: Tandem *N*-alkylation/vinylogous aldol reaction for the synthesis of 3-amino pyrones

Fang et al. demonstrated the umpolung chemistry of alkynyl 1,2-diketones **178** to access α -pyrones via NHC catalysis (**XV**) (Scheme 1.45). They have proposed that the *o*-acylated allenolate intermediate was formed in between the reaction. Also, a novel reaction route that included numerous group migrations and the formation of new bonds was proposed.¹¹⁵ As shown in Figure 1.9 the α -carbonyl group of **178** is reacted with carbene catalyst to form intermediate **A** and the *O*-acylated allenolate **B** is formed via first acyl transfer. Then, the nucleophilic addition of **B** or **C** to the second molecule of **178** afford **D**. Further, it will undergo second acyl transfer to generate intermediate **E**. Afterward, a unique acyloxy migration followed by lactonization led to α -pyrones. One C-C and three C-O bonds are formed in a single pot in this catalytic cycle.



Scheme 1.45: NHC-catalyzed umpolung of alkynyl 1,2-diketones

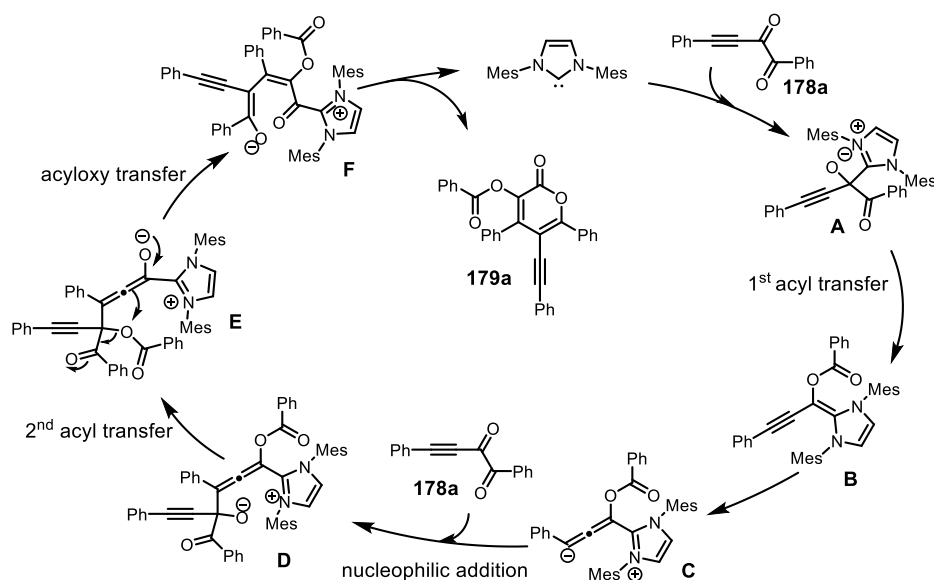
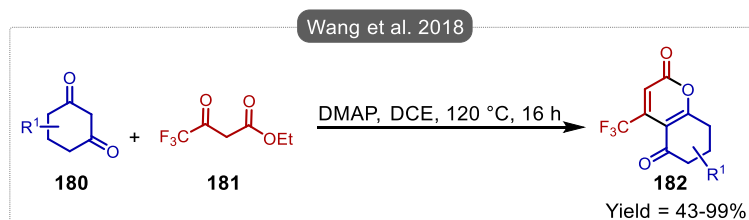


Figure 1.9: Proposed mechanistic cycle for unploung chemistry via NHC-catalysis

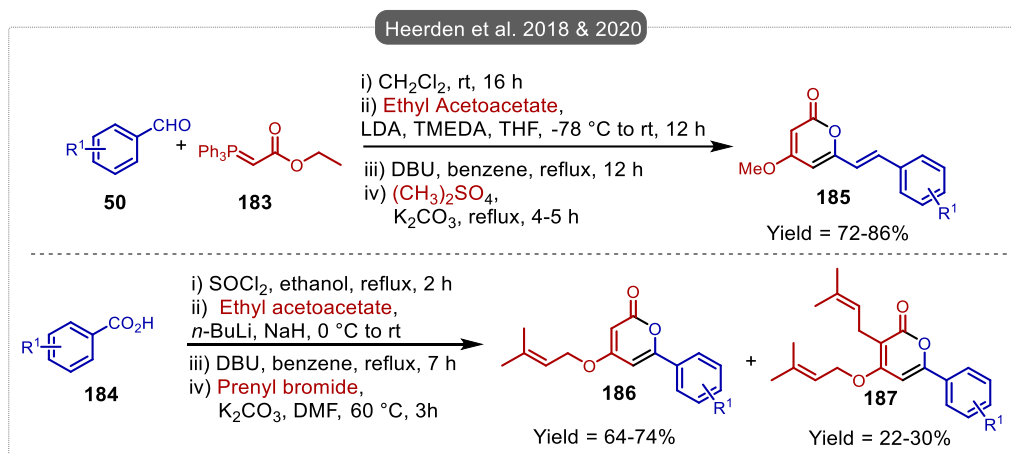


Scheme 1.46: Preparation of 4-trifluoromethyl 2-pyrone derivatives

In 2018, Wang's group demonstrated a Brønsted base-catalyzed Pechmann-type reaction of ethyl 4,4,4-trifluoroacetate **181** and cyclic 1,3-diones **180**. 4-trifluoromethyl substituted 2-pyrones **182** were isolated in excellent yields utilizing this approach (Scheme 1.46). In addition,

4-trifluoromethyl substituted 2-pyridones were also synthesized from this approach by using ammonium acetate as a source of ammonia.¹¹⁶

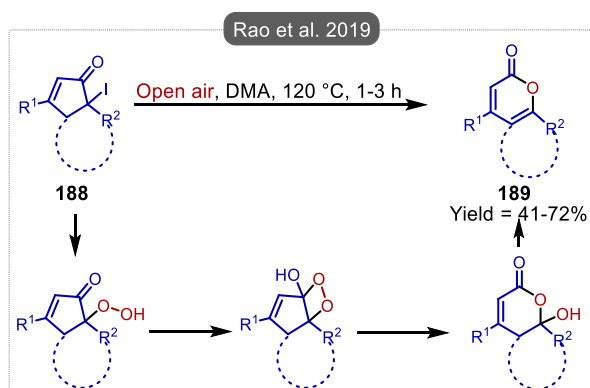
An efficient and catalyst-free 4-step sequential method for the synthesis of 6-styrenylpyrone **185** was developed by Obi and Heerden in 2018. Importantly, all the products were synthesized at gram scale. Utilizing the same approach, they have synthesized mono- and di-fluorosubstituted 5,6-dehydrokawain derivatives in high yield. In 2020, the same group have developed another 4-steps methodology for the synthesis of mono- **186** and di-prenylated 2-pyrone derivatives **187** (Scheme 1.47).¹¹⁷ Furthermore, the compounds were tested for their ability to inhibit the proliferation of bacteria, revealing that they display a significant activity. With *E. coli* being the most vulnerable of the test organisms, all the compounds were effective against one or more tested bacteria except the bromine-bearing analogs. Out of Eight derivatives, two derivatives, 4-(3-methylbut-2-enox)-6-phenyl-2*H*-pyran-2-one and 6-(4-fluorophenyl)-4-(3-methylbut-2-enox)-6-phenyl-2*H*-pyran-2-one have exceptional antibacterial activity against a drug-resistant β -lactamase-producing *Klebsiella pneumonia*, leading to the study of their potential synergy with ampicillin.



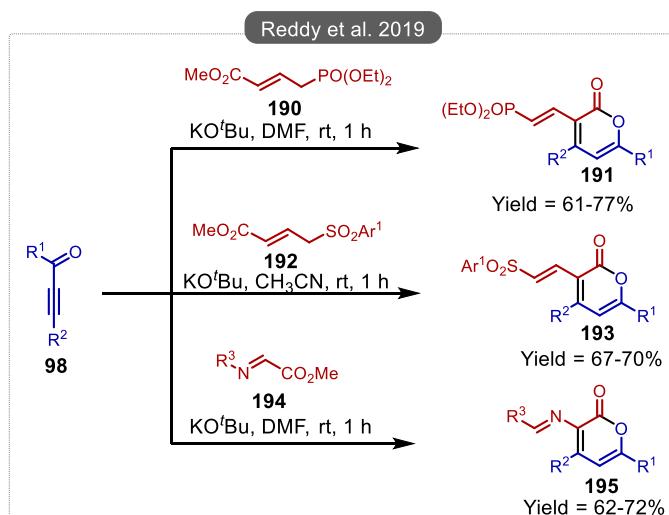
Scheme 1.47: Synthetic route to 5,6-dehydrokawain derivatives and prenylated 2-pyrones

Rao's group reported an effective method for developing α -pyrones, in which α -iodocyclopentenones **188** are subjected to a Baeyer-Villiger type oxidation in the absence of a catalyst or any additives (Scheme 1.48). Air is used as an environmentally safe oxidant in this process. Under mild reaction conditions, the reaction offers a straightforward and effective approach for constructing highly functionalized α -pyrones and demonstrates excellent functional group compatibility.¹¹⁸ The reaction goes via a well-known radical mechanism. The thermally induced C-I bond homolysis generates iodine as well as the alkyl radical which is trapped by oxygen to produce the peroxy radical. Next, the hydrogen abstraction from the solvent molecule is followed by intramolecular nucleophilic addition of the OOH group through a 4-exo-trig cyclization to give a bicyclic intermediate. It will undergo the 1,2-alkyl shift followed by dehydration to afford α -pyrones.

In the same year, Reddy's group demonstrated base-mediated successive vinylogous addition/cyclization reaction of ynones **98** and γ -phosphonyl/sulfonyl crotonates, which led to highly functionalized α -pyrones **191** and **193** (Scheme 1.49). The newly created olefin substituent at the C3-position of α -pyrone was found to have an exclusive *E*-geometry. In addition, the reaction of ynones with imine glyoxalates **194** and glycine imines produced 3-imino pyrones **195** under similar conditions.¹¹⁹

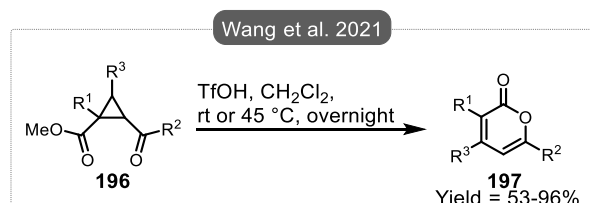


Scheme 1.48: Catalyst and additive-free Baeyer–Villiger oxidation for constructing 2-pyrones



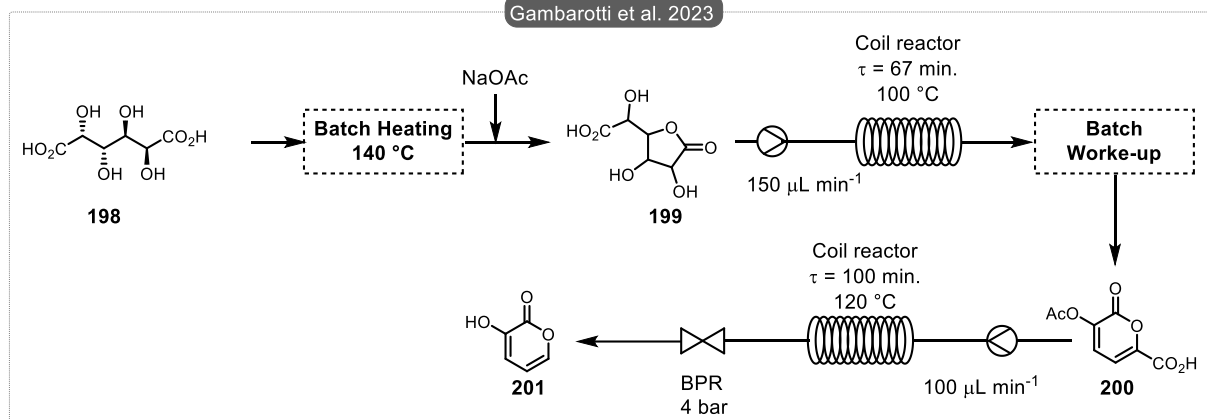
Scheme 1.49: Base-mediated cascade vinylogous addition/cyclization reaction

In 2021, Wang's group has developed a triflic acid-mediated ring expansion of 2-acylcyclopropane-1-carboxylates **196** for the synthesis of poly-substituted α -pyrones **197** (Scheme 1.50). In this developed method, the highly donating 1-aryl group is responsible for the cleavage of C-C bond of the donor-acceptor cyclopropane ring, which led to the 2-pyrone ring through lactonization.¹²⁰



Scheme 1.50: TfOH-mediated ring expansion of 2-acylcyclopropane-1-carboxylates

Recently, Gambarotti and co-workers have developed an efficient, novel, eco-friendly, and simple decarboxylation process to obtain the 3-hydroxy-2-pyrone **201** under continuous-flow conditions (Scheme 1.51). All methods were successfully established using a continuous flow system. In this two-step flow process, galactaric acid **198** is used as a starting material to access the 2-pyrones in high yield with significantly lesser time as compared to the batch process.¹²¹



Scheme 1.51: Continuous flow synthesis of 3-hydroxy-2-pyrone from galactaric acid

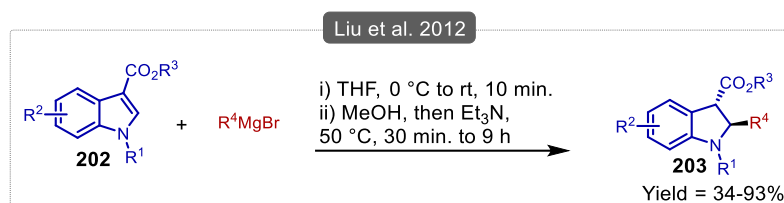
1.3 BRIEF LITERATURE REVIEW FOR THE SYNTHESIS OF DIHYDROINDOLES

Indole or indoline moieties, are one of the largest nitrogen-containing secondary metabolites,¹²² which are important structural motifs found in various natural products and biologically active compounds.¹²³ These compounds possess a fused ring systems that are characterized by the incorporation of an indole ring fused to a saturated ring, resulting in a bicyclic structure. The synthetic diversity of dihydroindoles (DHIs) or indolines not only provides access to structurally diverse compounds but also allows for the exploration of their biological activities and therapeutic potential.¹²⁴ Owing to the importance of indolines, their synthesis becomes an important area of current research. Several methods have been developed to construct diversely substituted dihydroindoles utilizing metal as well as organocatalysis.¹²⁵ Besides that, numerous synthetic modifications, oxidation, reduction, or functional group transformations were also demonstrated to synthesize indolines.¹²⁶ We have encapsulated here representative metal-free or organocatalyzed strategies for synthesizing DHIs.

1.3.1 Michael Initiated Reactions

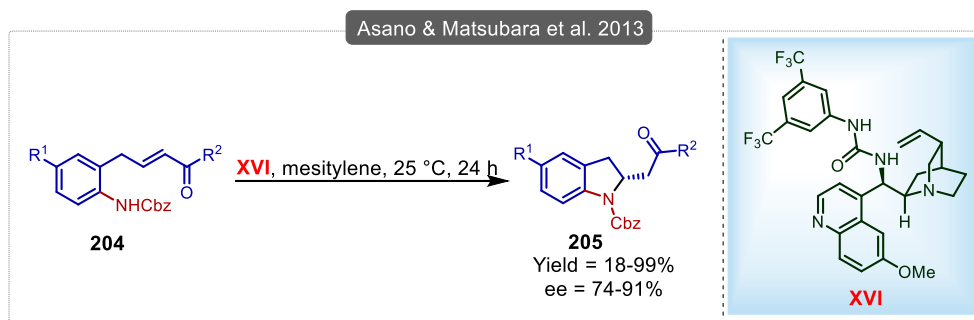
Michael addition reactions have been extensively exploited in organic synthesis because they are so versatile and have a wide range of applications.¹²⁷ In order to create complex compounds with desirable biological and physical features, the Michael addition reaction can introduce additional carbon-carbon bonds, chiral centers, and functional groups. These reactions involving the nucleophilic addition of a molecule with an active methylene group, known as a Michael donor, to a compound with an electron-deficient carbon-carbon double bond, known as a Michael acceptor, are referred to as Michael addition reactions. Numerous catalysts, including Lewis acids, transition metal complexes, and organocatalysts, can catalyze these reactions and have an impact on the reaction's kinetics, stereoselectivity, and regioselectivity.¹²⁸ Herein, we have enclosed metal-free Michael addition, addition-substitutions and double Michael addition reactions for the synthesis of dihydroindole derivatives. In addition, aza-alkylation followed by Michael addition reactions are also discussed.

In 2012, Liu and his group demonstrated the Michael addition reaction of Grignard reagents and 3-acylindoles **202** (Scheme 1.52). The Michael adduct indolines were isolated in a stereoselective manner, and the enolate intermediates with stereospecific quaternary carbon core might be trapped using aryl acyl chlorides.¹²⁹ Further, products were transformed into indoles via DDQ oxidation in a one-pot fashion.



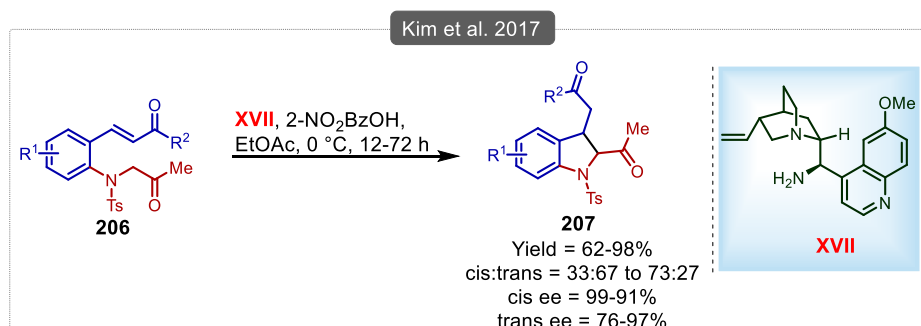
Scheme 1.52: Synthesis of indolines through the nucleophilic addition reactions of Grignard

Miyaji, Asano and Matsubara devised an asymmetric intramolecular aza-Michael reaction of α,β -unsaturated ketones **204**. *Cinchona*-derived bifunctional amino-urea catalyst (**XVI**) was found suitable to catalyze the reaction by hydrogen bond activation to afford 2-substituted indolines (Scheme 1.53).¹³⁰ The deprotection of the Cbz-group was also examined by using H_2 , Pd/C in the mixture of ethanol and dichloromethane.



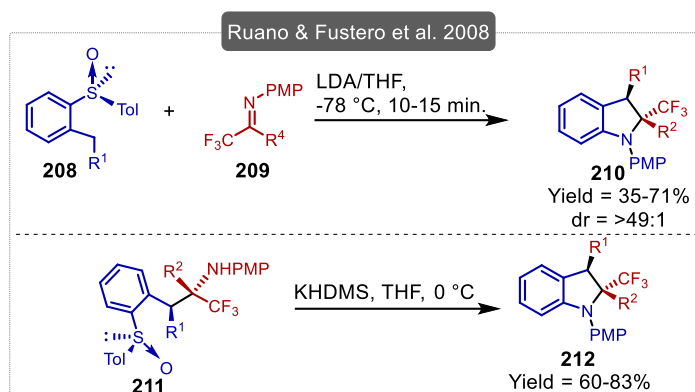
Scheme 1.53: Synthesis of asymmetric indolines via intramolecular aza-Michael addition reaction

Kim's group reported another organocatalyzed asymmetric intramolecular Michael addition reaction in 2017 (Scheme 1.54).¹³¹ The reaction was catalyzed by *Cinchona*-derived primary amine catalyst (**XVII**) leading to 2,3-disubstituted dihydroindoles **207** in high yield and moderate diastereoselectivity. The reaction proceeds via enolate chemistry. Importantly, it was found that the *cis*-product was predominant when R^2 is an aryl group. However, with alkyl group (R^2), *trans*-indolines were afforded efficiently.



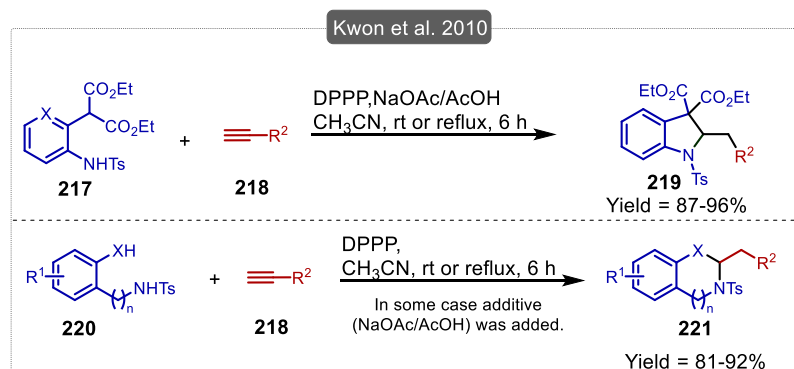
Scheme 1.54: *Cinchona*-derived primary amine catalyzed synthesis of asymmetric indolines

In 2008, Ruano and Fustero have developed an anionic-anionic asymmetric tandem reaction for constructing optically pure fluorinated indolines **210** with one or more stereogenic centers. In this tandem approach, 2-(*p*-toluenesulfinyl) alkylbenzenes **208** were directly reacted with *N*-PMP-fluorinated imines **209** in the presence of LDA (Scheme 1.55). The fundamental characteristic of this protocol was an intramolecular NSR of a *p*-tolylsulfinyl group by the amide anion.¹³² They isolated the intermediate product **211** and subjected to substitution reaction by using KHDMS as a base, resulting trisubstituted indolines **212** efficiently (Scheme 1.55).



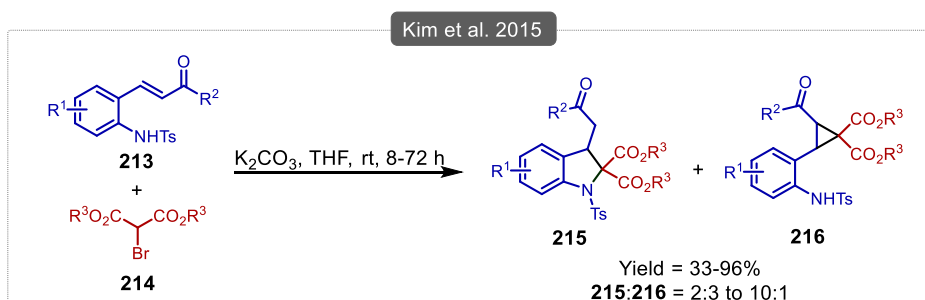
Scheme 1.55: One-pot synthesis of fluorinated indolines via addition and $\text{S}_{\text{N}}\text{Ar}$ reaction

Sriramurthy and Kwon demonstrated DPPP (diphenylphosphinopropaned) catalyzed mixed Michael-Michael reaction of dinucleophiles **217** and electron-deficient acetylenes **218** (Scheme 1.56). Several benzannulated *N*-heterocycles **219** and **221** i.e., indolines, benzimidazolines, benzomorpholines, dihydropyrrolopyridines, tetrahydroisoquinolines, tetrahydroquinolines, and dihydrobenzo-3,1-oxazines were synthesized under metal-free conditions utilizing a standard protocol.¹³³ In this approach, they have synthesized seven different types of benzannulated *N*-heterocycles by using DPPP as a catalyst with the utilization of acetic acid or ammonium acetate as an additive in some reactions. All the benzannulated *N*-heterocycles were isolated in excellent yield.



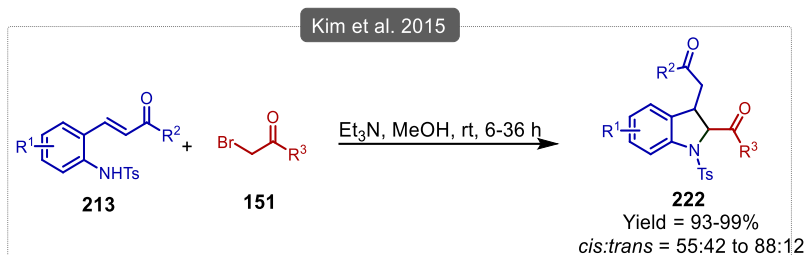
Scheme 1.56: A unified synthesis of diverse heterocycles via Michael-Michael reaction

Kim and co-workers established a base-catalyzed cascade Michael/aza-cyclization reaction of *ortho*-aminochalcones **213** and dialkyl bromomalonates **214** (Scheme 1.57). A wide range of highly functionalized 2,3-disubstituted indolines were synthesized under optimized conditions in good yields.¹³⁴ They proposed that the chemoselective formation of indoline is preferable via Michael addition followed by aza-cyclization. On the other hand, the formation of a cyclopropane ring was followed a different path. After Michael addition, it will undergo α -alkylation.



Scheme 1.57: Chemo-selective synthesis of indolines via a domino Michael/aza-cyclization reaction

In 2015, Yu, Kim developed an efficient base-mediated stereoselective aza-alkylation/Michael cascade reaction of *o*-amino chalcones **213** with α -bromoacetophenones **151** (Scheme 1.58).¹³⁵ This cascade methodology afforded highly functionalized *cis*-indolines **222** in high yields with moderate diastereoselectivities. The reaction proceeds via *N*-alkylation followed by intramolecular Michael addition through enolate formation. Furthermore, the structure of *cis*-indolines were confirmed by NOESY analysis.

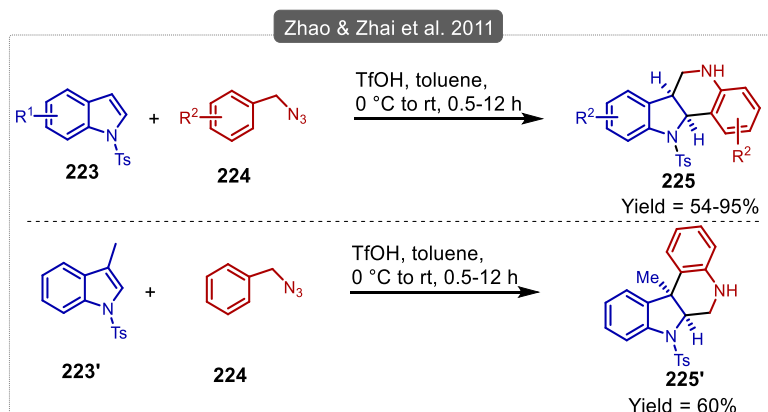


Scheme 1.58: Chemoselective synthesis of *cis*-2,3-disubstituted dihydroindoles

1.3.2 Cycloaddition or Annulation Reactions

Cycloaddition or annulation reactions have been used extensively in the construction of a variety of natural products as well as in pharmaceuticals.¹³⁶ Many methods have been established utilizing this type of reaction to synthesize dihydroindole derivatives. In this context, we have addressed selective transition metal-free annulation reactions.

Song, Zhao, and Zhai demonstrated a formal [4+2] cycloaddition reaction of benzyl azides **224** with indoles **223** to assemble tetrahydro-5*H*-indolo[3,2-*c*]quinolones **225** (Scheme 1.59). The cascade reaction implicated through benzyl azide-to-iminium rearrangement and two consecutive Pictet-Spengler reactions to afford tetracyclic products in moderate to exceptional yields.¹³⁷ In this reaction, azide **224** generates iminium ion **A** via the protonation followed by rearrangement by loss of molecular nitrogen. This iminium ion **A** is trapped by **223** through the formation of a C-C bond, preferably at C-3 of **223**, followed by cyclization at C-2 of **223**, which leads to the desired product **225** via two sequential Pictet-Spengler reactions (Figure 1.10). In contrast, when the reaction was carried out with the 3-methylated indole derivatives **223'**, a regioisomeric product **225'** was formed through a formal [4+2] cycloaddition. In this, a methyl group blocked the C-3 position of indole. Thus, an intramolecular Pictet-Spengler reaction took place at C-2 to produce intermediate **C**, which was then cyclized to produced **225'**.



Scheme 1.59: Acid-catalyzed synthesis of tetrahydro-5*H*-indolo[3,2-*c*]quinolone

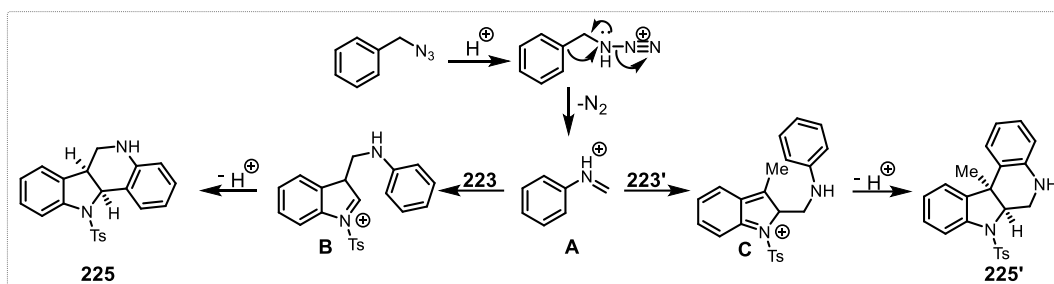
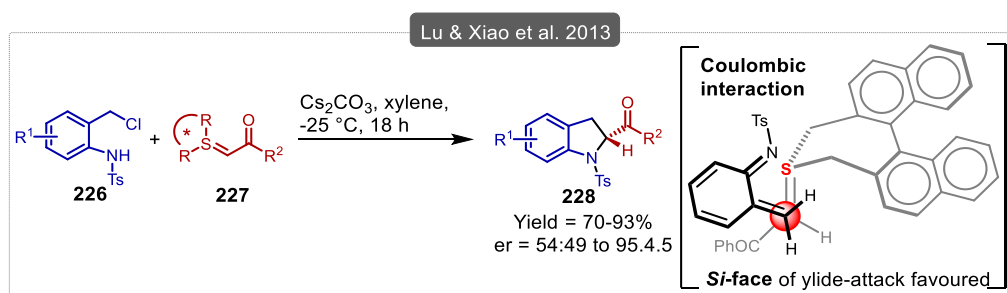


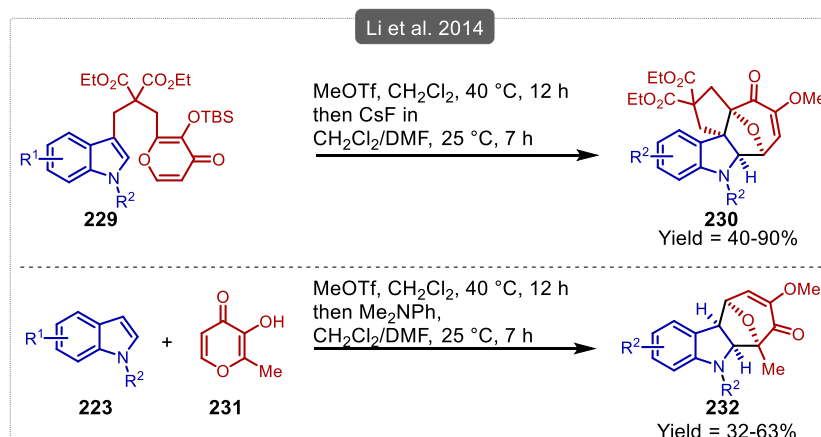
Figure 1.10: Proposed mechanism for the formation of **225** and **225'**

In 2013, Lu and Xiao et al. established an asymmetric [4+1] cycloaddition reaction of *N*-(*ortho*-chloromethyl)aryl amides **226** with chiral sulfur ylides **227** (Scheme 1.60). This protocol allowed to construct 2-substituted indolines in viable yields and enantioselectivities.¹³⁸ In this cascade method, chiral sulfur ylide is approached from the *Si*-face to the in situ generated unsaturated imine during Michael addition. Therefore, the steric effect between the naphthyl ring of chiral ylide and sulfonamide moiety of **226** is minimal.



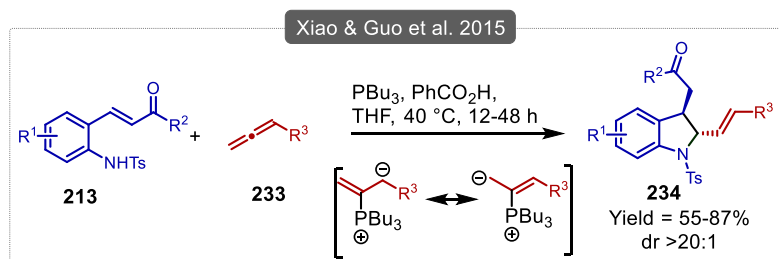
Scheme 1.60: Synthesis of 2-substituted asymmetric indolines via [4+1] cycloaddition reaction

In the subsequent year, Li and co-workers have devised the first dearomative [5+2] cycloaddition reaction of indole with an oxidopyrylium ylide **231** (Scheme 1.61). Several highly functionalized and synthetically demanding oxacyclohepta[b]indoles **230** were synthesized utilizing this protocol. Furthermore, DFT studies were carried out to evaluate the mechanistic insight of this for the formation of *endo*-cycloaddition products in [5+2] annulation reactions.¹³⁹ It was calculated that the free-energy barrier for the *endo*-pathway is 15.6 kcal mol⁻¹ is lower than that *exo*-pathway. Notably, the energy of the *exo*-cycloaddition product is 22.9 kcal mol⁻¹ is higher than the *endo*-cycloaddition product agreed to the stability of the *endo*-cycloaddition product. Next, the intermolecular dearomative [5+2] cycloaddition reaction was also tested by using indole **223** and maltol **231** under similar conditions. Pleasingly, the reaction occurred smoothly to afford a variety of indole derivatives **232** having tetracyclic core.



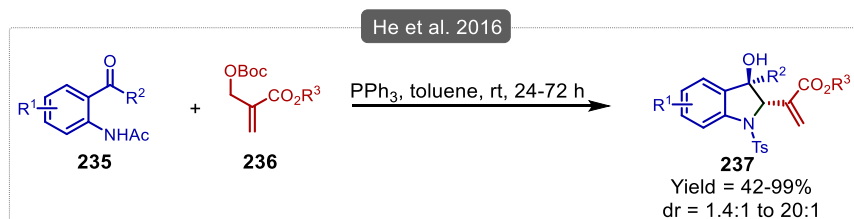
Scheme 1.61: Synthesis of oxacyclohepta[b]indoles via intramolecular [5+2] cycloaddition reaction

In 2015, Xiao and Guo et al. have reported an efficient [4+1] annulation reaction to synthesizing *trans*-2,3-disubstituted indolines. 2-Tosylaminochalcones **213** and allenates **233** were used as reacting partners for this phosphine-catalyzed annulation reaction (Scheme 1.62).¹⁴⁰ The Lewis acid phosphine reacts with allenates **233** to generate a zwitterionic intermediate that will undergo [4+1] annulation reaction to afford **234**. Furthermore, the reaction was found to be efficient at the gram scale.



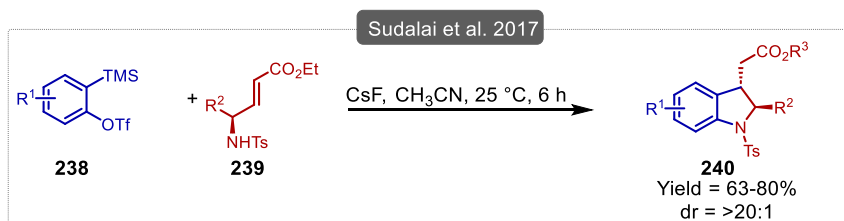
Scheme 1.62: Phosphine-catalyzed [4+1] annulation of allenates with *o*-aminochalcones

Another facile and efficient phosphine-catalyzed [4+1] annulation reaction of ester-modified allylic carbonates **236** and *o*-aminophenyl ketones **235** were demonstrated by He and coworkers (Scheme 1.63). 2,3-Disubstituted dihydro-indole derivatives in high yield and dr were synthesized under optimized conditions utilizing this approach.¹⁴¹ In addition, they have synthesized 3-hydroxy-2,3-disubstituted dihydro-benzofurane derivatives efficiently under similar conditions by using *o*-hydroxy chalcones instead of *o*-aminophenyl ketones. Additionally, CuSO_4 was used to convert the annulation products into functionalized indoles and benzofurans.



Scheme 1.63: [4+1] Annulation reaction of ester-modified allylic carbonates and *o*-aminophenyl ketones via phosphine catalysis

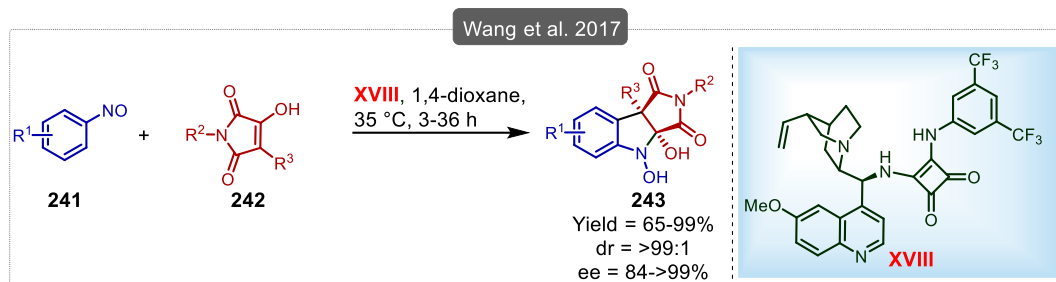
In 2017, Aher, Suryavanshi, and Sudalai developed a one-step formal [3+2]-annulation approach for the construction of substituted dihydroindoles (Scheme 1.64).¹⁴² In this cycloaddition reaction, γ -amino- α,β -unsaturated esters **239** and in-situ generated aryne were used as a three-atom and two-atom synthon respectively. COSY and NOESY studies assigned the relative stereochemistry of products.



Scheme 1.64: [3+2] Cycloaddition of unsaturated γ -tosyl amino esters with arynes

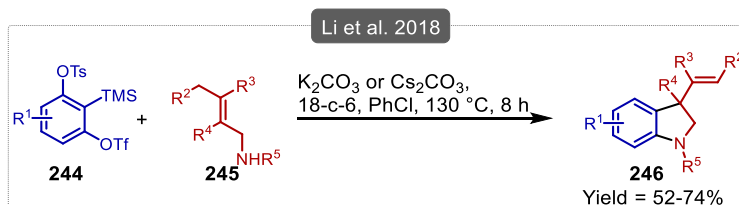
Wang and co-workers have synthesized chiral quaternary *N*-hydroxyindolines **243** via an enantioselective annulation reaction of nitrosoarenes **241** and hydroxymaleimides **242** (Scheme

1.65). The [3+2] annulation reaction was catalyzed by a *Cinchona*-derived bifunctional squaramide-amine catalyst leading to two adjacent quaternary stereocenters with multifunctional groups bearing chiral *N*-hydroxyindolines in excellent yields and stereoselectivities.¹⁴³ Furthermore, the effectiveness and potentials of this annulation reaction and the chiral target entities are effectively illustrated by delicate conversions to a range of new chiral indolines.



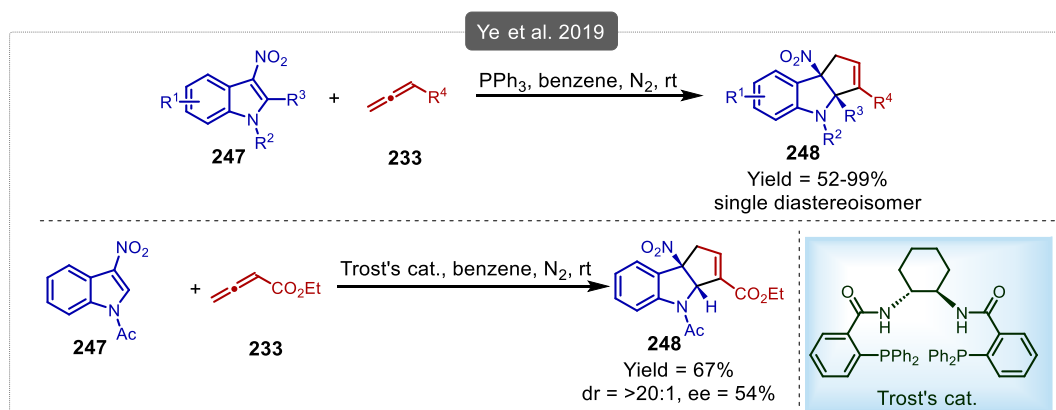
Scheme 1.65: Stereoselective synthesis of chiral *N*-hydroxyindolines

In 2018, Li's group have developed an efficient transition-metal-free aryne annulation reaction via nucleophilic-ene domino sequence for the synthesis of benzo-fused *N*-heterocyclic scaffolds **246** (Scheme 1.66).¹⁴⁴ Altering the leaving ability of the second leaving group on 1,2-benzdiyne equivalents showed the advantage of this domino method. They have synthesized indoline derivatives and other *N*-containing heterocycles utilizing this domino approach. This research expanded the chemistry of 1,2-benzdiyne equivalents, as well as opened a new path for aryne annulation.



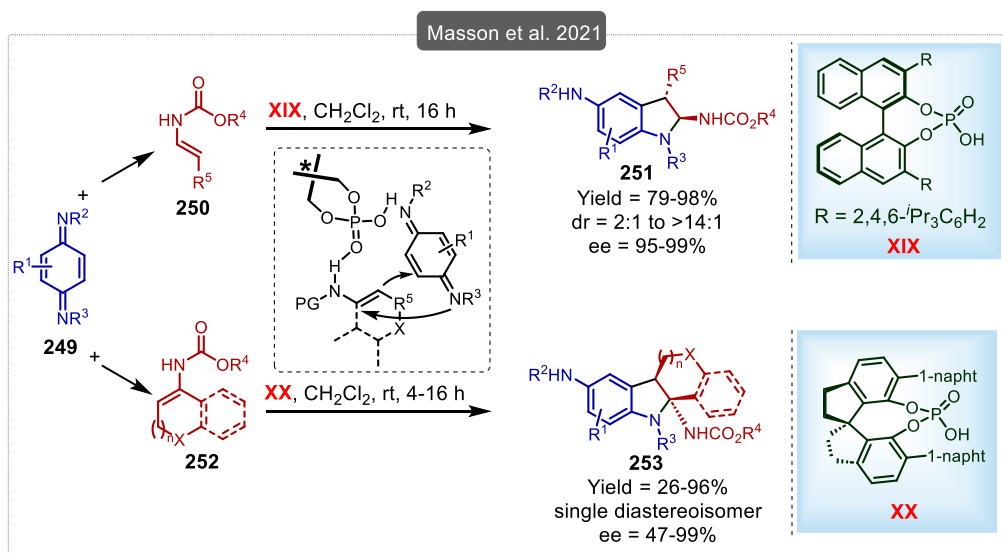
Scheme 1.66: Synthesis of benzo-fused *N*-heterocyclic scaffolds

Another phosphine-catalyzed annulation reaction of allenolate was reported by Ye and co-workers in 2019. In this reaction, allenolates undergo [3+2] cycloaddition reaction with 3-nitroindoles **247** to access cyclopenta[*b*]indolines **248** in good to excellent yields with high dr (Scheme 1.67).¹⁴⁵ Furthermore, 2-nitrobenzothiophene and 2-nitrobenzofuran were also explored as dearomative [3+2] annulation partners. In addition, the asymmetric dearomative [3+2] cycloaddition reaction was also tested by using Trost's phosphine catalyst with similar conditions. The desired product were isolated in 67% yield with >20:1 dr and 54% ee.



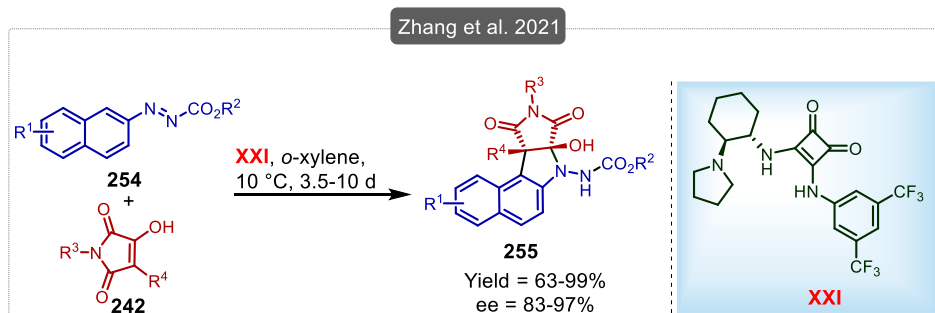
Scheme 1.67: Phosphine-catalyzed [3+2] annulation of allenoates with 3-nitroindoles

In 2021, Masson et al. have reported BINOL- (**XIX**) and SPINOL- (**XX**) derived phosphoric acid-catalyzed regio- and enantio-selective formal [3+2] cycloaddition reaction of quinone-diimides **249** with β -substituted ene- and thioenecarbamates **250** as well as cyclic enamides **252** (Scheme 1.68).¹⁴⁶ A broad range of 2,3-disubstituted 2-aminodihydroindoles, including polycyclic ones, were synthesized in high yields with moderate to complete diastereoselectivities and excellent ee. Furthermore, the absolute configuration of products was confirmed by single crystal X-ray analysis and the Cbz-group of the product was successfully removed by using Pd/C in the water-methanol mixture at 70 °C.



Scheme 1.68: BINOL- and SPINOL- derived phosphoric acid-catalyzed formal [3+2] cycloaddition reaction

Recently, another *Cinchona*-derived bifunctional squaramide-amine catalyzed asymmetric dearomative [3+2] annulation of 3-hydroxymaleimides **242** were reported by Zhang's group (Scheme 1.69). In this cycloaddition reaction, they have used azonaphthalenes **254** as a three-atom synthon with 3-hydroxymaleimides. The reaction relies on Michael addition followed by aromatization/acetalization (Figure 1.11). The asymmetric induction has occurred in the first step. The enolate of 3-hydroxymaleimides will undergo 1,4-conjugate addition with **254** to generate (*S*)-configured intermediate **A**. Next, it will undergo subsequent steps to afford chiral indolines. Furthermore, one of the succinimide fused indoline was treated with triethylsilane under different conditions, yielding two types of reductive products in considerable yields and enantioselectivity.¹⁴⁷



Scheme 1.69: Stereoselective synthesis of diversely substituted succinimide fused indolines

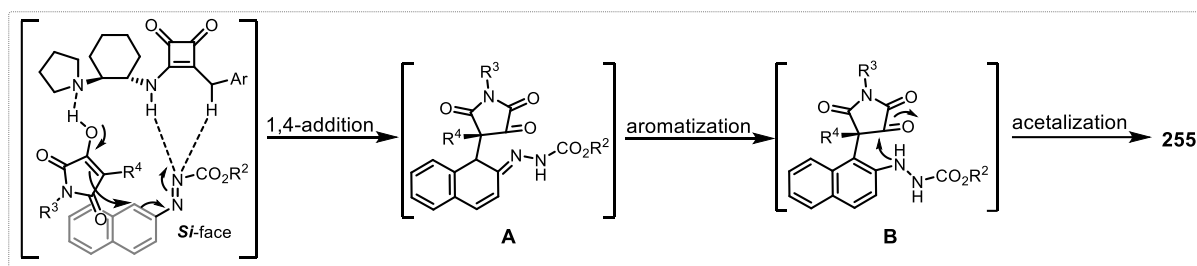


Figure 1.11: Plausible mechanism for bifunctional-amine catalyzed asymmetric dearomative [3+2] annulation

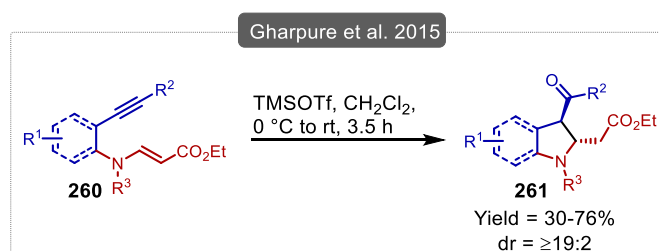
1.3.3 Mannich Reactions

The Mannich reaction is a versatile and widely used method for the formation of C-N and C-C bonds. It provides an efficient route to introduce the necessary amine functionality into the indole ring system. This introduction serves as a key step in the construction of dihydroindoles, enabling access to a diverse array of substituted derivatives with significant biological activities. In this context, we have represented the application of Mannich reactions in the synthesis of dihydroindoles and highlighted some notable examples in the field.

In 2015, Tantillo and Smith et al. demonstrated an approach to the stereoselective synthesis of two chiral centers bearing indolines via a Mannich-like 5-*endo*-trig process (Scheme 1.70).¹⁴⁸ The reaction proceeded smoothly in the presence of quinine-derived ammonium salt (**XXII**) and CsOH·H₂O yielding disubstituted dihydroindoles **257** and **259** in viable yield with excellent diastereo- and enantio-selectivity. In this Mannich-type reaction, they have proposed that zwitterionic quinine-derived moiety is a key catalytic species produced by deprotonation of an ammonium salt with the anionic reaction product and that protonation plays an efficient role to controlling enantioselectivity. They also suggested that the reaction would only occur in the organic phase. Therefore, rather than being a phase-transfer-catalyzed activity, the reaction may be better defined as a phase-transfer-initiated one. This result may have significance for the mechanistic routes followed by other PTC-mediated processes.

Scheme 1.70: Asymmetric synthesis of indolines via a Mannich-like 5-*endo*-trig process

In the same year, Gharpure, Prasath and Kumar established the synthesis of *trans*-2,3-disubstituted dihydroindoles via intramolecular alkyne iminium ion cyclization reaction of vinylogous carbamates **260** (Scheme 1.71). The reaction was catalyzed by Lewis's acid, trimethylsilyl trifluoromethanesulfonate.¹⁴⁹ In addition, pyrrolidine derivatives were also synthesized by applying this approach to *N*-protected homopropargyl amines derived vinylogous carbamates. Notably, the regioselectivity of the alkyne iminium ion cyclization could be altered by utilizing an internal nucleophile, hydroxy group, resulting cyclic ether-fused 1,2-dihydroquinolines. Importantly, the entire synthesis of *N*-heterocycle can also be completed in a single pot, starting with *ortho*-iodo aniline derivatives.

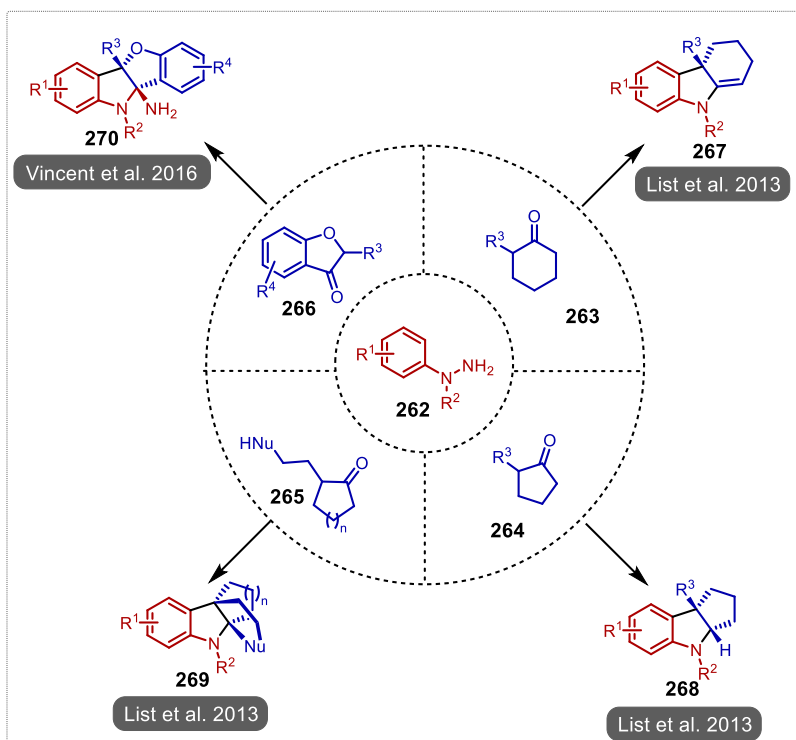


Scheme 1.71: Lewis acid-catalyzed alkyne iminium ion cyclization reaction of vinylogous carbamates

1.3.4 Fisher Indolization Reactions

Fischer indolization reaction is a well-established method for the synthesis of dihydroindoles.¹⁵⁰ In this reaction, an aldehyde or ketone and a primary amine are transformed into an indole derivative via the formation of an imine intermediate. The reaction is typically carried out under acidic conditions and can be catalyzed by Lewis acids. Some important Fischer indolization reactions for constructing DHIs are shown in Scheme 1.72.

In 2013, List and co-workers demonstrated an asymmetric Fischer indolization reaction of mono-substituted cyclic ketones **263-265** (Scheme 1.72). The reaction was catalyzed by chiral Brønsted acid (*R*)-STRIP to afford highly diverse chiral indolines with significant structural complexity.¹⁵¹ The approach has been further expanded to synthesize complex propellanes having two vicinal quaternary stereocenters by employing tethered nucleophile-containing substrates via the enantioselective indolization/ring-closing cascades process. The mechanism of this asymmetric Fischer indolization is shown in Figure 1.12.



Scheme 1.72: Synthesis of indoline derivatives via Fisher indolization reaction

In 2016, Vincent et al. demonstrated Fischer indolization methodologies for constructing benzofuro[3,2-*b*]indolines **270** (Scheme 1.72).¹⁵² To overcome the development of a highly tense imine at the ring junction of the indoline and benzofuran portions, the elimination of ammonia was stopped during the Fischer reaction. The addition of nucleophiles to the aminal site is likely prevented by the unfavorable production of the imine. Further, the activation of the phenoxy substituent in the presence of trifluoroborane allowed for the addition of allyl nucleophiles to the nearby tetrasubstituted carbon at the ring junction. An Umpolung of this nucleus is represented by the formation of an electrophilic character at the C3-position of the indole portion. As a result, they have created organic fluorescent materials, 3,3-disubstituted indolenines.

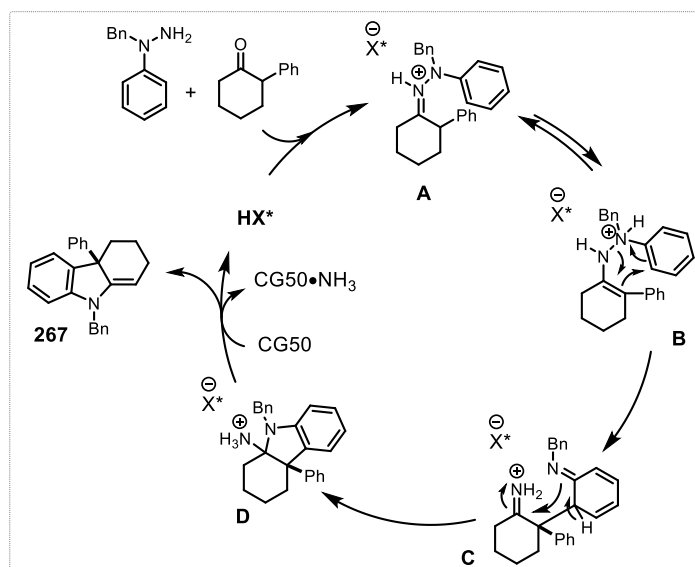
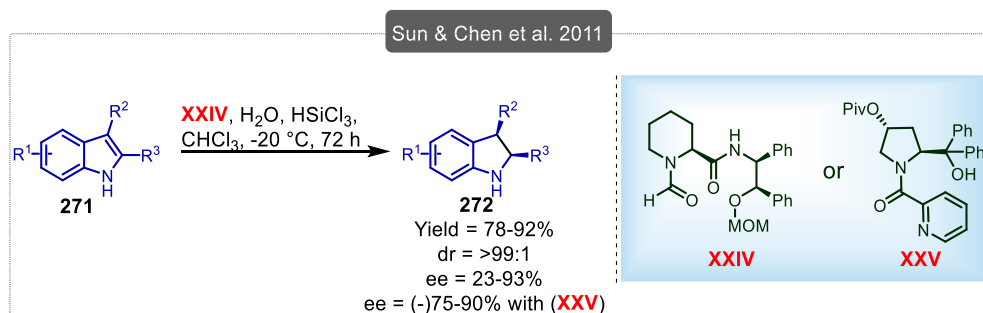


Figure 1.12: Mechanistic cycle for asymmetric Fischer indolization

1.3.5 Miscellaneous Reactions

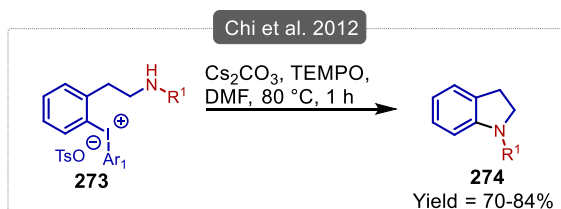
In this section, we have discussed organocatalyzed halo-amino cyclization, halocyclization of indoles, and addition followed by cyclization-type reactions for the synthesis of dihydroindoles.

In 2011, Sun and Chen et al. reported the first organocatalytic direct enantioselective reduction reaction of 1*H*-indoles to afford chiral indolines **272** (Scheme 1.73). The reaction proceeds via C3 protonation with the in-situ formed HCl acid to generate electrophilic indolenium ions, followed by chiral Lewis base-promoted asymmetric hydrosilylation with HSiCl_3 .¹⁵³ Several chiral indolines were successfully synthesized in up to 93% enantioselectivity. Remarkably, the 2,3-disubstituted ones showed exclusive diastereocontrol.



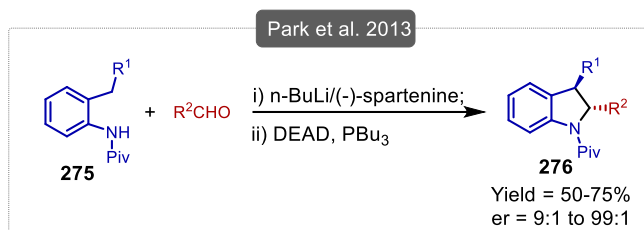
Scheme 1.73: Combined Brønsted acid and Lewis base promoted asymmetric hydrosilylation of indoles

Next year, Chi et al. efficiently constructed an indoline scaffold via intramolecular nucleophilic amidation reaction of a diaryliodonium salt **273** (Scheme 1.74). These were prepared by effective transformation of diacetoxystannarene compounds into Koser's reagent intermediates and then reaction with arylstannanes. In this ring closure reaction, substituted diaryliodonium salts were treated with Cs_2CO_3 and TEMPO to afford distinct *N*-protecting groups bearing indolines in considerable yield.¹⁵⁴



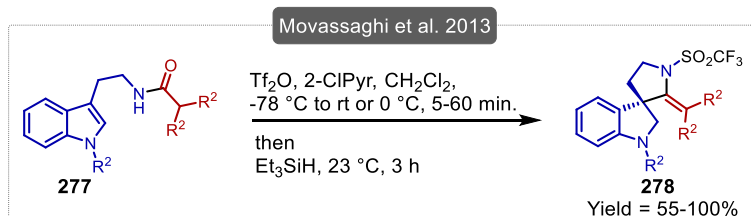
Scheme 1.74: Intramolecular nucleophilic amidation reaction of diaryliodonium salts

Y. S. Park group have demonstrated the Mitsunobu cyclodehydration reaction of the amino alcohols, generated from ($\pm$)-sparteine promoted lithiation-substitution reaction of *o*-alkyl *N*-pivaloyl aniline **275** (Scheme 1.75).¹⁵⁵ This cyclodehydration reaction was carried out with the combination of DEAD and PBU₃ in acetonitrile as a solvent to afford enantiopure *trans*-2,3-disubstituted dihydroindoles.



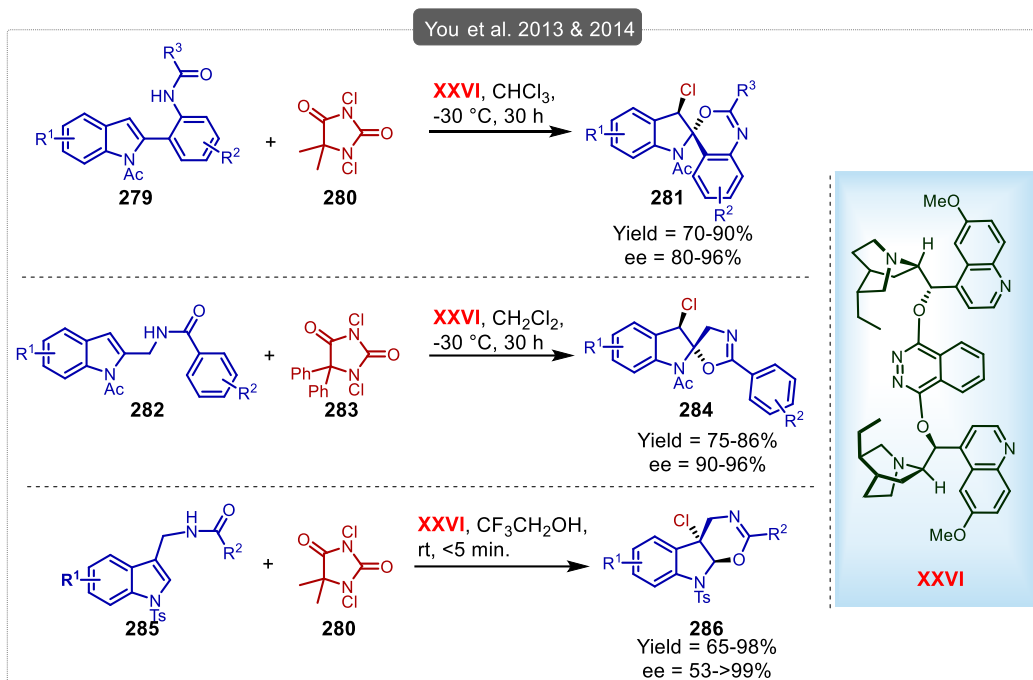
Scheme 1.75: Mitsunobu cyclodehydration reaction of *N*-pivaloyl amino phenethyl alcohol

In 2013, Medley and M. Movassaghi devised the Bischler-Napieralski reaction of *N*-acyltryptamines **277** for the synthesis of spiro-pyrrolidinoindolines **278** (Scheme 1.76). The reaction proceeded through intramolecular addition at C2 nucleophiles by forming spiroindoleninium ion intermediates. The developed methodology was highly resilient to Wagner-Meerwein rearrangements.¹⁵⁶ They have synthesized several polycyclic spiro-pyrrolidinoindolines derivatives by utilizing this approach.



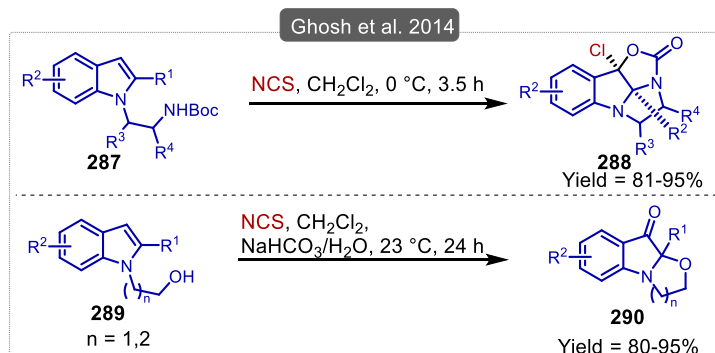
Scheme 1.76: Synthesis of spiro-pyrrolidinoindolines through Bischler-Napieralski reaction

Yin and You reported an enantioselective chlorocyclization reaction of indole-derived benzamides **279** and **282** in the presence of (DHQD)₂PHAL catalyst (Scheme 1.77).¹⁵⁷ Continuous quaternary and tertiary carbon centers containing spiro-indolines were synthesized in high yield and excellent enantioselectivities. In this cyclization reaction, the catalyst plays two distinct roles. First, increase the amide group's nucleophilicity by hydrogen bonding with phthalazine nitrogen. Secondly, the activation of chloronium species by tertiary amine nitrogen provides the chiral environment for asymmetric induction. In 2014, they also developed chlorocyclization of indole-3-yl-benzamides **285** by using the same catalyst for the synthesis of fused indolines **286** (Scheme 1.77).¹⁵⁸ Importantly, the 1% of the catalyst is sufficient for constructing enantiopure indolines in excellent yield.

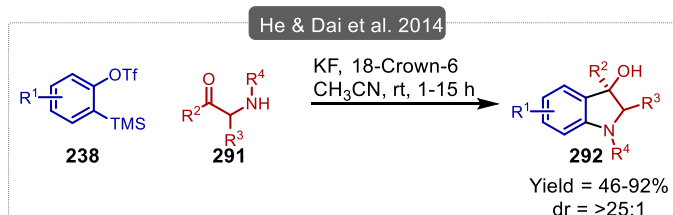


Scheme 1.77: (DHQD)₂PHAL catalyzed asymmetric synthesis of spiro-indolines

In 2014, Ghosh and Chen et al. established cascade halogenation followed by intramolecular *N/O*-nucleophilic cyclization reaction for the synthesis of aza-3-oxaindolines **288** and (Scheme 1.78). This method is efficient to construct a wide range of tri- and tetracyclic indolines in high yields.¹⁵⁹ Further, the structure of the halogenation/cyclization product was confirmed by single crystal X-ray analysis. In addition, they have developed halogenation followed by intramolecular *O*-nucleophilic cyclization reaction for the synthesis of tricyclic tetrahydro-1,3-oxazino[3,2-*a*]indoles and tetrahydrooxazolo[3,2-*a*]indoles.



Scheme 1.78: Cascade halogenation/intramolecular nucleophilic cyclization reaction of 2-aryl indoles

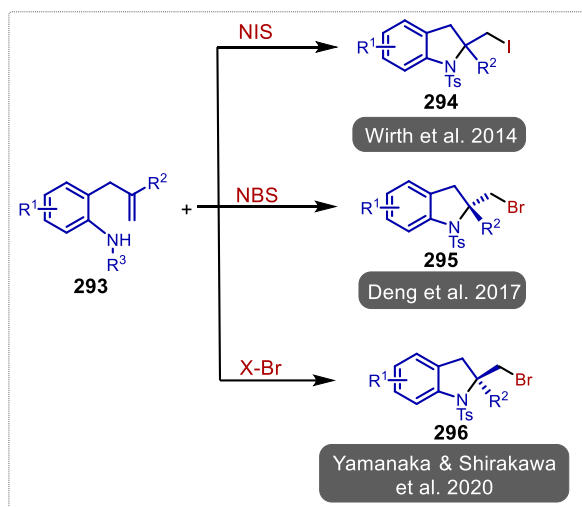


Scheme 1.79: Coupling reaction of arynes with α -amino ketones

In the same year, He and Dai's group demonstrated cascade insertion-cyclization reaction of α - or β -amino ketones **291** with in-situ generated arynes (Scheme 1.79).¹⁶⁰ *Syn*-selectivity multi-

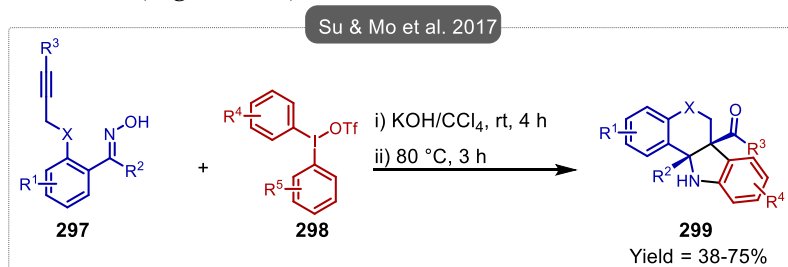
substituted indolines **292**. In addition, *N*-aryl tetrahydroquinolines were also synthesized from the coupling reaction of arynes with α -amino ketones and β -amino ketones respectively by utilizing this tandem approach.

Wirth and co-workers demonstrated an organocatalyzed stereoselective iodo-amination reaction of alkenes. The reaction was catalyzed by a chiral thiohydantoin-derived thiourea catalyst. The authors have studied a few aryl derivatives at *para*-position of 2-allylanilines **293** under optimized conditions. Pleasingly, iodomethyl-substituted indolines were formed in moderate yield with good enantioselectivities (Scheme 1.80).¹⁶¹ Deng et al. have demonstrated another enantioselective halo-amination reaction by using *N*-bromosuccinimide (NBS) with allyl aniline. BINAP(S) monosulfide is used as a catalyst for this asymmetric bromo-amination reaction to afford the range of chiral 2-bromomethyl substituted indolines **295** (Scheme 1.80).¹⁶² Furthermore, the products were transformed into synthetically valuable compounds. In 2020, Yamanaka and Shirakawa et al. have also developed a chiral bifunctional sulfide-catalyzed enantioselective bromoamino cyclization reaction. 2-(Bromomethyl)indoline derivatives were synthesized from *N*-(*p*-biphenylsulfonyl)-2-allylaniline **293** substrates in the presence of phenyl urea scaffold containing BINOL-derived chiral bifunctional sulfide catalyst. Further, computational studies were conducted to demonstrate the source of high stereoselectivities of developed bromoamino cyclization reactions. (Scheme 1.80).¹⁶³



Scheme 1.80: Synthesis of indolines via haloaminocyclization reactions

Su and Mo's group have reported *N*-arylation/cycloaddition/[3,3]-rearrangement reaction of alkynyl tethered oxime **297** and diphenyl iodonium triflate **298** under metal-free conditions (Scheme 1.81). The one-pot cascade reaction proceeded through selective *N*-arylation to alkynyl tethered oxime to yield alkynyl tethered nitrones, then an intramolecular (3+2) cycloaddition/[3,3]-sigmatropic rearrangement in a regioselective manner to provide 2,3-quaternary fused indolines (Figure 1.13).¹⁶⁴



Scheme 1.81: One-pot cascade synthesis of 2,3-quaternary fused indolines

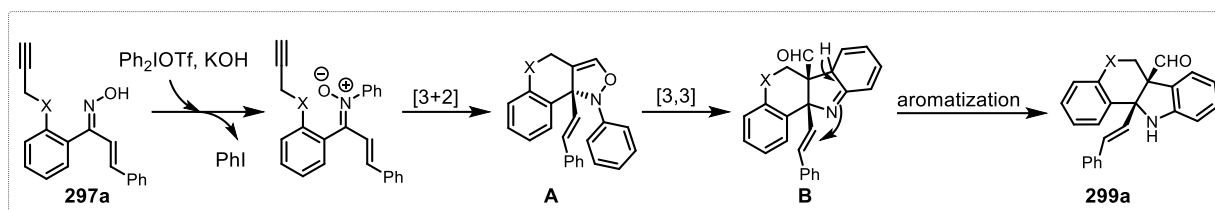
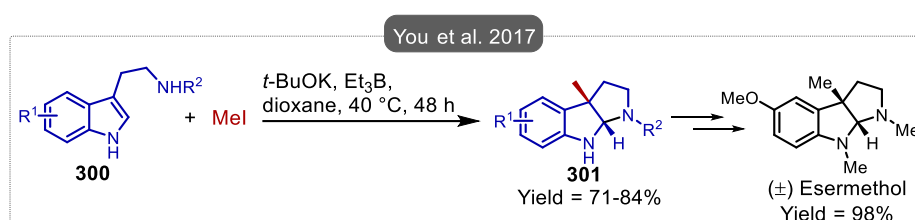


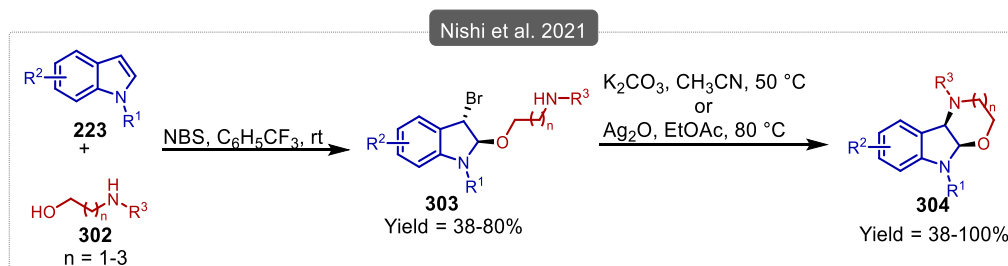
Figure 1.13: Plausible mechanism of *N*-arylation/cycloaddition/[3,3] rearrangement reaction

An efficient cascade dearomatization reaction of indole derivatives **300** in the presence of methyl iodide was reported by You and co-workers (Scheme 1.82). This cascade approach allowed to construct pyrroloindolines **301** and furoindolines having methyl-substitution at C3 position. The doubly methylated pyrroloindolines were formed via methylative dearomatization followed by *N*-methylation reactions. Further, the developed method was used for the synthesis of (±)-Esermethol.¹⁶⁵

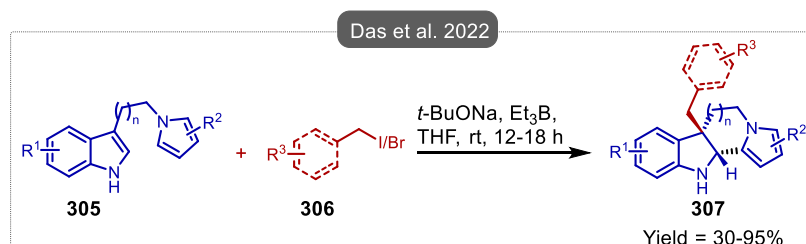


Scheme 1.82: Synthesis of C3-methyl substituted pyrroloindolines and furoindolines

In 2021, Nishi et al. have devised halo-etherification/cyclization reaction of *N*-protected indoles **223** (Scheme 1.83). They have synthesized six- to eight-membered 2,3-fused indoline and azaindoline derivatives in viable yield via intramolecular annulation reaction of halo-etherification product.¹⁶⁶



Scheme 1.83: Synthesis of 2,3-fused indoline heterocycles via halo-etherification/cyclization reaction



Scheme 1.84: Synthesis of *cis*-diastereoselective 2,3-fused tetracyclic indolines

Recently, Das et al. have developed a cascade C3-alkylation/aza-Friedel–Crafts alkylation reaction of indole C-3 tethered pyrroles (Scheme 1.84).¹⁶⁷ This is the first example for the synthesis of an all-carbon quaternary stereocenter at C-3 position containing tetracyclic *cis*-indolines **307**

via dearomative indole C-3-allylation/benzylation of indole-tethered pyrroles. The reaction was promoted by the combination of NaO^tBu/Et₃B base to went intramolecular alkylation followed by aza-Friedel–Crafts ring closure in a regioselective manner. The reaction has a board substrate scope. The relative stereochemistry of products was assigned by X-ray single crystal analysis.

1.4 BRIEF LITERATURE REVIEW FOR THE SYNTHESIS OF BENZOXAZOLE

Benzoxazole is a dual heteroatom containing heterocyclic compound that possesses a fused benzene and oxazole ring system. It is widely found in various natural products, pharmaceuticals, and biologically active molecules, making it an essential structural motif in medicinal chemistry and drug discovery.¹⁶⁸ Several synthetic methods have been developed, providing efficient routes for the preparation of benzoxazoles with different substitution patterns. One of the commonly employed strategies for benzoxazole synthesis involves the condensation of *ortho*-aminoaryl ketones/aldehydes with nitriles or amides.¹⁶⁹ Another important method for benzoxazole synthesis is the oxidative cyclization of *ortho*-hydroxyaryl amides/amines.¹⁷⁰ Furthermore, transition metal-catalyzed reactions have also emerged as a significant tool for benzoxazole synthesis.¹⁷¹ Other synthetic methods, including microwave-assisted synthesis, multicomponent reactions, and rearrangement reactions, have been explored.¹⁷² Hearin, we have abridged some representative metal-free reports on the synthesis of benzoxazole by using *ortho*-aminophenol is one of the reacting synthons.

1.4.1 Annulation Reactions

A variety of methods, including metal-catalyzed and metal-free approaches have been demonstrated for constructing benzoxazoles via annulation reactions.¹⁷³ The most common method for the annulation of benzoxazoles involves the use of palladium or copper catalysis.¹⁷⁴ Apart from that, metal-free approaches to the annulation of benzoxazoles have also been developed.¹⁷⁵ It involves the condensation of *ortho*-aminophenol with an appropriate aldehyde, carboxylic acid, or its derivative, such as an acid chloride or anhydride, in the presence of a dehydrating agent. The reaction is typically carried out under acidic or basic conditions and can be catalyzed by Lewis acids or Brønsted acids. We have addressed some important acid, base, and NHC catalyzed as well as oxidative annulation reactions for the synthesis of benzoxazole derivatives from *ortho*-aminophenols.

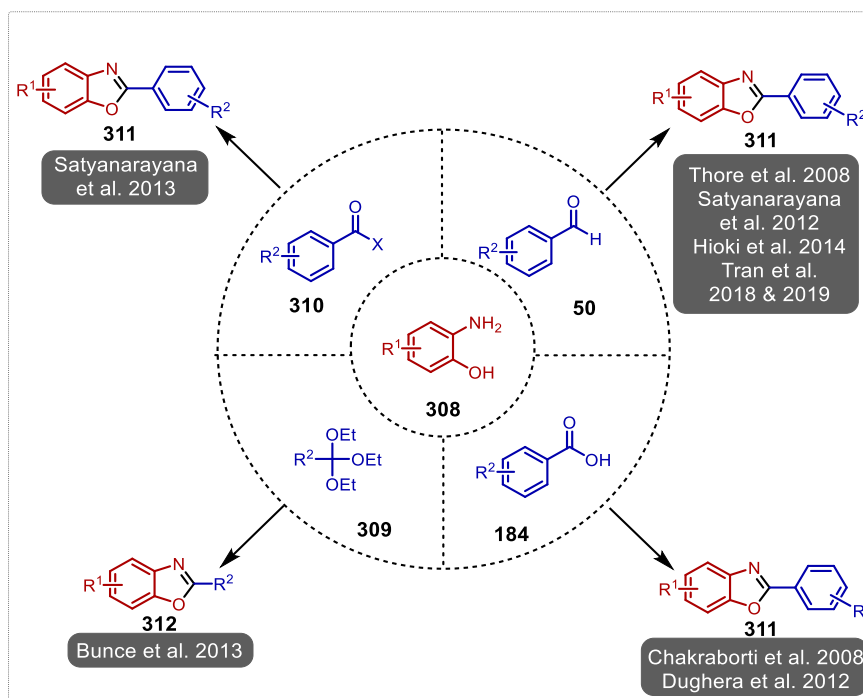
1.4.1.1 Acid-Catalyzed Annulation

Several research groups have explored the acid-catalyzed annulation reactions for the synthesis of benzoxazole derivatives (Scheme 1.85). In 2008, Thore and coworkers have used alum (KAl(SO₄)₂·12H₂O) as a novel acid catalyst for constructing 2-arylbenzoxazole **311** derivatives from the condensation/cyclization reaction of several substituted aldehydes **50** with *ortho*-aminophenols **308**.¹⁷⁶ The reaction was proceeded efficiently in water as a solvent with an inexpensive and widely accessible catalyst to afforded benzoxazole derivatives in good to excellent yields. Further, Stayanarayana et al. have demonstrated the application of a silica-supported NaHSO₄ catalyst for the synthesis of benzoxazole derivatives from similar starting materials.¹⁷⁷ The reaction was carried out in the presence of dioxane as a solvent under reflux conditions. In continuation of their work, the same catalyst was applied to *o*-substituted anilines and acyl chlorides **310** under solvent-free conditions.¹⁷⁸ The reaction was proceeded well to afford corresponding benzoxazole, benzimidazole and benzothiazole derivatives in high yields. Hioki and co-workers have utilized an alkoxyamine linker for TFA-catalyzed solid-phase synthesis of benzoxazoles, quinazolines, and quinazolinones.¹⁷⁹ The reaction relied on sequential reactions on the solid support. Firstly, aromatic aldehydes **50** were anchored on aldoxime linkage. Secondly, the intermediate products were cleaved under acidic conditions with paraformaldehyde to produce the corresponding aldehydes, which were then subjected to oxidative coupling with 2-substituted anilines in the air to yield the desired compounds.

In 2018, Tran's group has developed an efficient and environmentally friendly condensation reaction of *o*-aminophenol, *o*-phenylenediamines, and *o*-aminothiophenols, with

aldehydes. The reaction was catalyzed by a homogeneous catalyst, phosphonium acidic ionic liquid to access diversely substituted 2-arylbenzoxazole, 2-arylbenzimidazole, and 2-arylbenzothiazole derivatives in favorable yield.¹⁸⁰ The catalyst triphenyl(butyl-3-sulphonyl)phosphonium toluene sulfonate can be synthesized through a one-pot synthesis from easily accessible starting material. Interestingly, the catalyst was found to be efficient after the fourth recovery. Next year, they have demonstrated a heterogeneous reusable catalyst, BAIL gel, for constructing benzoxazoles, benzimidazoles, and benzothiazoles. The catalyst can be synthesized by treating 1-methyl-3-(4-sulfobutyl)-1*H*-imidazolium hydrogen sulphate with TEOS.¹⁸¹ The transplantation of the BAIL onto the surface of TEOS increased the material's catalytic activity and facilitated the recovery of the catalyst from the reaction mixture.

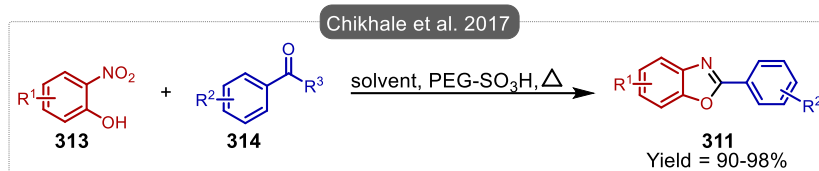
The annulation chemistry of aryl acids **184** and their derivatives with *ortho*-aminophenols were also explored by several researchers (Scheme 1.85). In 2008, Chakraborti et al. have developed methane sulfonic acid-catalyzed one-pot synthesis of 2-substituted benzoxazole from the reaction of aromatic acids with *ortho*-substituted anilines.¹⁸² The reaction proceeded via direct condensation/cyclization reaction of *ortho*-aminophenols with in-situ generated acid chlorides. The scope of the reaction was very broad in terms of variety of substituted acids and aminophenols. Barbero, Cadamuro, and Dughera have also developed the synthesis of various benzo-fused azoles by the reaction of *ortho*-substituted anilines with several acid derivatives and aldehydes.¹⁸³ The developed reaction was catalyzed by *ortho*-benzenedisulfonimide as a homogenous catalyst and the catalyst was recycled and reused for the next cycle. In 2013, an ammonium chloride-catalyzed efficient approach was demonstrated by Bunce and coworkers for the synthesis of benzoxazole, benzimidazole, and benzothiazole derivatives.¹⁸⁴ In this methodology *ortho*-substituted anilines reacted with *ortho*-esters under mild conditions in the presence of water or ethanol as a solvent to afford benzo-fused products in high yields.



Scheme 1.85: Selective examples of acid-catalyzed annulation reactions of *ortho*-aminophenols

Chikhale and coworkers have established highly efficient and sustainable approach for the synthesis of substituted benzoxazole derivatives (Scheme 1.86). They have developed two methods: the first one is the reaction of 2-nitrophenols **313** with benzaldehyde derivatives in chloroform as a solvent, the second method involves the reaction of 2-nitrophenols **313** with carboxylic acid derivatives in the presence of chloroform:dioxane (1:1) as a solvent mixture. Both

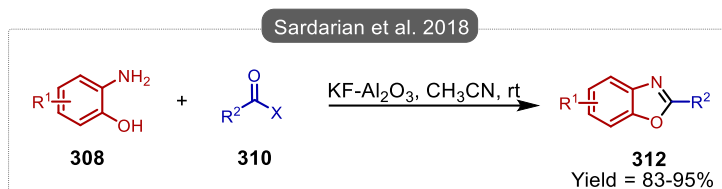
approaches proceeded smoothly in the presence of an economical and reusable catalyst, poly (ethylene glycol)-supported sulphonic acid (PEG-SO₃H), with low catalyst loading.¹⁸⁵



Scheme 1.86: PEG-SO₃H catalyzed synthesis of benzoxazole derivatives

1.4.1.2 Base-catalyzed annulation

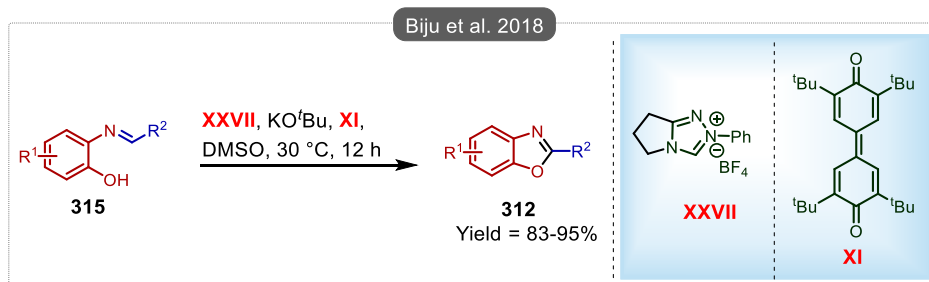
Bahadorikhalili and Sardarian have demonstrated the first heterogenous base-catalyzed synthesis of benzoxazole derivatives. KF-Al₂O₃ is used as a catalyst for the annulation reaction of *ortho*-aminophenols **308** with acyl chlorides or acid anhydrides **310** (Scheme 1.87).¹⁸⁶ The generality of the developed approach was demonstrated by using a variety of aliphatic and aromatic carboxylic acid derivatives containing electron-donating or withdrawing substituents. This novel base-catalyzed approach was also effective for constructing 2-substituted benzothiazoles in high yields under mild reaction conditions. Significantly, by escaping the purification steps, all the products were isolated in pure form after filtration and the catalyst was recycled multiple times.



Scheme 1.87: Heterogenous base catalyzed synthesis of benzoxazole derivatives

1.4.1.3 NHC catalyzed annulation

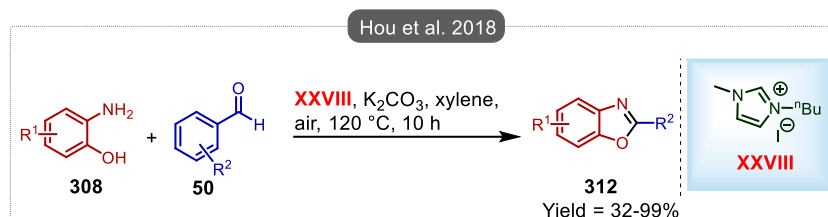
In 2018, Biju and coworkers have developed NHC (**XXVII**) catalyzed intramolecular cyclization of aldimines **315**, which were prepared from the reaction of 2-aminophenols with aromatic aldehydes. The reaction provided an easy excess to 2-arylbenzoxazole derivatives **312** (Scheme 1.88). The reaction proceeded through the formation of aza-Breslow intermediates from imines and NHC. The presence of oxidative conditions allowed to form the key imidoazolium intermediate which subsequently underwent intramolecular cyclization to afford the benzoxazoles in high yields. The reaction had a wide variety of functional groups tolerance.¹⁸⁷



Scheme 1.88: NHC catalyzed intramolecular cyclization reaction of aldimines

In the same year, Hou et al. successfully employed in-situ generated NHC (**XVIII**) as a low-cost and effective catalyst for the aerobic oxidative synthesis of 2-substituted benzoxazoles (Scheme 1.89). Readily available *N*-heterocyclic imidazolium salt generated active catalyst NHC

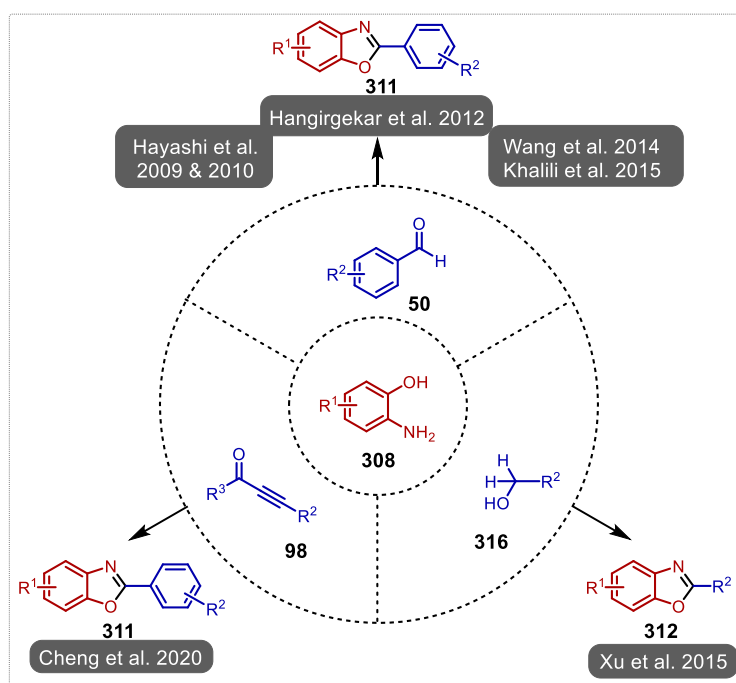
in situ in the presence of a base. Further, the developed method was applied to construct benzothiazoles and benzimidazoles ¹⁸⁸



Scheme 1.89: NHC catalyzed condensation reaction for the synthesis of benzoxazoles

1.4.1.4 Oxidative annulation

Numerous oxidative condensation/cyclization¹⁸⁹ reactions of *ortho*-aminophenols with carbonyl compounds **50** and various aryl, heteroaryl and alkenyl alcohols **316** were also discussed (Scheme 1.90). In 2009, Hayashi et al. reported a one-pot oxidative cyclization reaction of 2-aminophenol and substituted aldehydes. In this one-pot reaction, an activated carbon-molecular oxygen system facilitated the dehydrogenation step. The cyclization of intermediate phenolic Schiff base led to benzoxazole derivatives was confirmed by a detailed mechanistic study. Further, it was also mentioned that activated carbon is recoverable and reusable.¹⁹⁰ In continuation, next year, they have synthesized benzoxazole containing potential medicine JTP-426467 for metabolic syndrome in three steps.¹⁹¹ Another one-pot oxidative cyclization reaction of 2-aminophenols and benzaldehydes for the synthesis of 2-substituted benzoxazoles was developed by Hangirgekar. The reaction was catalyzed by phenyl-trimethyl-ammonium tribromide.¹⁹²

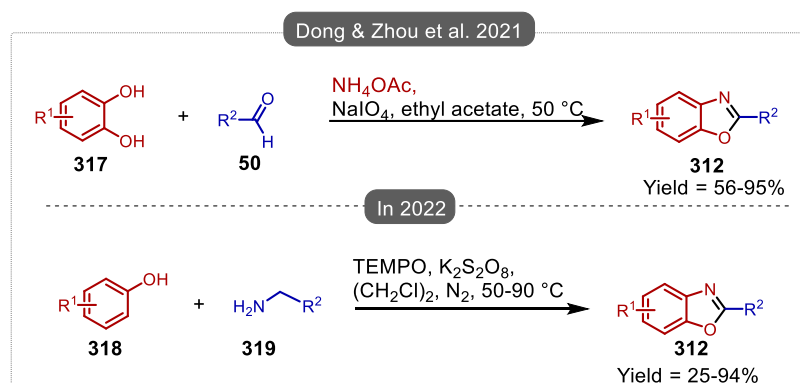


Scheme 1.90: Oxidative annulation reactions of *ortho*-amino phenols with carbonyls and alcohols

In 2014, Wang et al. have established a highly efficient, simple, and environmentally friendly method for synthesizing benzoxazoles and benzothiazoles in the presence of mesoporous poly(melamine-formaldehyde) heterogeneous organocatalysts.¹⁹³ This inexpensive, green, readily available, and recyclable catalyst facilitated the oxidative cyclization reaction of *ortho*-substituted aminobenzenes with different aldehydes in an O₂ atmosphere. The catalyst can be simply recovered by filtration and reused multiple times without losing catalytic activity.

Khalili and Banazadeh have described simple and efficient condensation reactions of aldehydes and *o*-substituted anilines. In addition, benzoxazoles were also prepared via one-pot oxidation/condensation of alcohols with 2-amino-(thio)phenol/anilines. In this tandem approach, graphene oxide (GO) is used as a heterogeneous bifunctional reagent for sequential oxidation and condensation steps. Further, benzimidazole and benzothiazole derivatives were also synthesized by applying this approach to the reaction of 2-amino-thiophenol/anilines with alcohols.¹⁹⁴ Xu et al. have used easily accessible alcohols with *ortho*-substituted anilines for constructing benzoxazole derivatives. They have developed ^tBuONa-catalyzed an effective, useful, environmentally friendly direct aerobic oxidative cyclo-condensation reaction for the synthesis of benzoxazoles.¹⁹⁵ The high reactivity and effectiveness of this remarkably simple and useful cyclo-condensation method are explained by mechanistic investigations which revealed that *o*-substituted anilines promoted the initial aerobic alcohol-oxidation step. In 2020, an acid-mediated C-C double bond breaking of enaminone followed by a new C-O bond formation has been devised for the synthesis of benzoxazole derivatives. Initially, the air was used as an oxidant. Further, NCS or NFSI as oxidants were also tested for oxidative cleavage of C-C double bond of *N*-(2-hydroxyphenyl) enaminone. The reaction has wide functional group tolerance.¹⁹⁶

Recently, Dong and Zhou et al. have successfully established a metal- and additive-free synthesis of benzoxazoles using catechols **317**, aldehydes, and ammonium acetate. A wide variety of benzoxazoles, including fluorescent whitening agent OB, JTP- 426467, bi- and trimeric benzoxazoles, and tafamidis analogues, were synthesized efficiently.¹⁹⁷ The mild reaction conditions allows sensitive functional group tolerance. The reaction proceeded presumably via a curious aminocyclohexadiene alcohol intermediate. The developed method was efficient for large-scale synthesis. In continuation, they have demonstrated a metal-free oxidative-annulation reaction of accessible amines **319** and phenols **318** for the synthesis of benzoxazole derivatives. A modular phenol functionalization is accomplished by TEMPO. The developed method was compatible for a wide range of functional groups, leading to functionally and structurally distinct diverse benzoxazoles. In addition, authors have developed a practical synthesis for the drug tafamidis.¹⁹⁸ The synthesis was more efficient in terms of selectivity, efficiency, and atom- and step-economies over traditional methods. Furthermore, it confirmed that the radical adducts of TEMPO with *ortho*-2,4-cyclohexadien-1-one radicals acted as intermediaries.

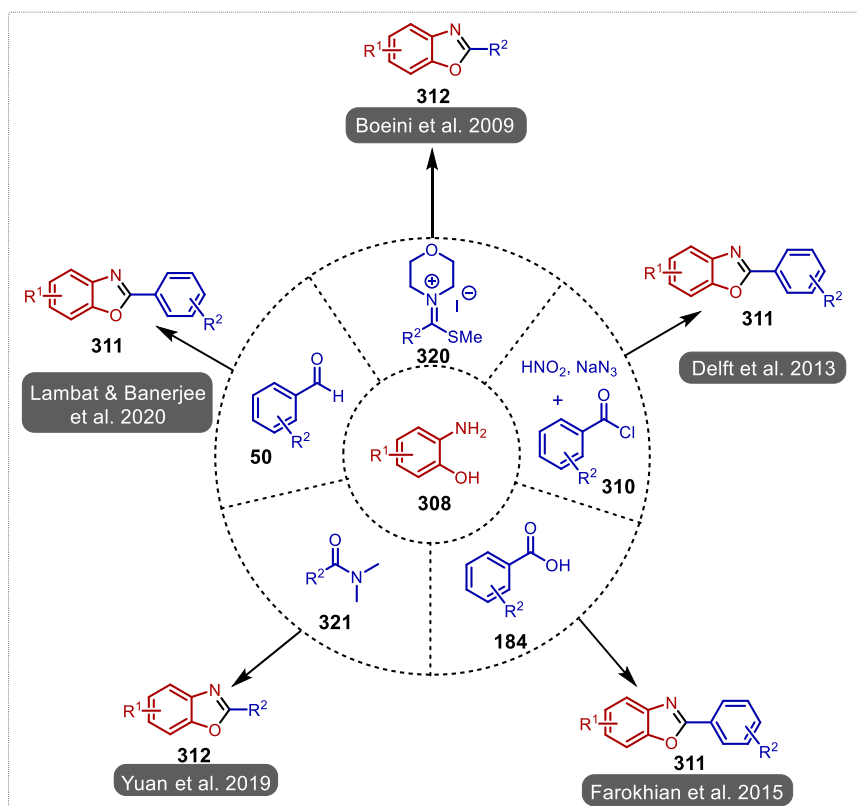


Scheme 1.91: Synthesis of benzoxazoles from phenol derivatives

1.4.2 Miscellaneous Reactions

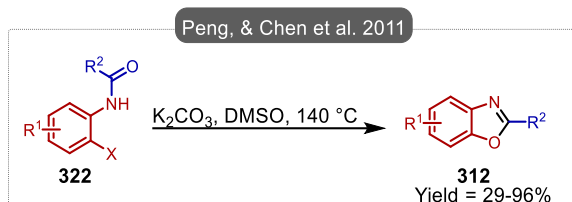
Several reports on the synthesis of benzoxazoles from *ortho*-aminophenols by using a variety of organocatalysts were abridged here (Scheme 1.92). In 2009, Boeini and Najafabadi established a one-step aquatic reaction of 2-aminophenols and thioamidinium salts **320** for the synthesis of benzoxazoles. The reaction was catalyzed by hexadecyltrimethylammonium bromide salt to afford benzoxazole derivatives in good to excellent yields. Further, the method was applied to the synthesis of benzimidazole and benzothiazole derivatives.¹⁹⁹ After that, phosphane catalyzed Staudinger/aza-Wittig reaction sequence was developed by Delft et al. for

the synthesis of benzoxazole derivatives. The required starting materials for this sequence were prepared separately via a two-step procedure involving i) diazotization followed by nucleophilic aromatic substitution with sodium azide to form 2-azidophenol, ii) acylation with an acid chloride. The reaction sequence is based on the in situ reduction of 5-phenyldibenzophosphole imine by diphenylsilane via regeneration of the catalyst. They also proposed that the fast aza-Wittig cyclization played significant role in order to minimize challenging P=N bond reduction.²⁰⁰ In 2015, Nikpassand, Fekri and Farokhian have demonstrated ionic liquids catalyzed synthesis of new benzoxazoles from the reaction of various salicylic acid **184** derivatives and 2-amino-4-chlorophenol. The catalyst (3,3-(butane-1,4-diyl)bis(1,2-dimethyl-1*H*-imidazole-3-ium) bromide {[BDBDIm]⁺Br⁻} works well at the room-temperature.²⁰¹ The developed method provides several benefits, including solvent-free conditions, good yields, a straightforward process, comfortable conditions, and minimal environmental impact. Further, the ionic liquid was recovered and reused. Yuan's group have described a novel, effective, metal-free, and cost-effective method for producing 2-substituted benzoxazoles and benzothiazoles from 2-amino-(thio)-phenols and DMF derivatives **321** in the presence of imidazolium chloride without the use of additional catalysts or additives. The reaction provides high yields of the desired products and have a broad substrate application.²⁰² In 2020, rice husk-derived chemically activated carbon catalyzed condensation reaction of 2-amino-(thio)-phenol, and *ortho*-phenylene diamine with aromatic aldehydes was reported by Lambat and Banerjee et al. The reaction proceeded efficiently at room temperature in the presence of aqueous ethanol as a solvent. A wide range of benzoxazole, benzothiazole, and *N*-benzimidazole derivatives were synthesized. The catalyst was easily filtered out of the reaction mixture and recycled up to eight cycles.²⁰³



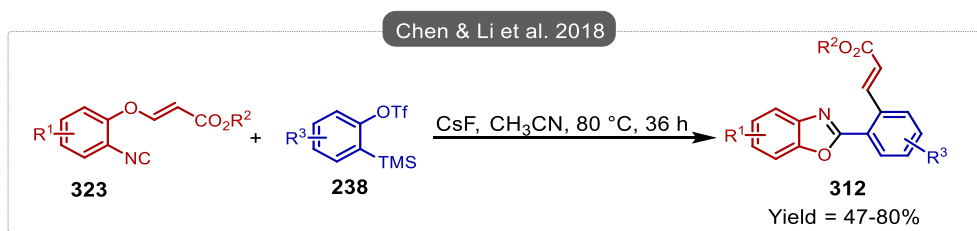
Scheme 1.92: Application of acid or acid derivatives in the synthesis of benzoxazoles

Peng and Chen et al. have demonstrated a direct base-mediated intramolecular C–O bond formation reaction of *o*-haloanilides **322** for the synthesis of benzoxazole derivatives (Scheme 1.93). The intramolecular cyclization reaction was carried out with 2.0 equiv. of K₂CO₃. In this approach, the C–O bond was formed via the formation of a benzyne intermediate followed by nucleophilic addition.²⁰⁴



Scheme 1.93: Synthesis of benzoxazole via intramolecular C–O bond formation reaction of o-haloanilides

Chen and Li et al. have developed a domino reaction of arynes with 2-isocyanophenyloxyacrylate **323** to construct a benzoxazole ring with an olefin fragment into the aryne ring (Scheme 1.94). This strategy involves nucleophilic addition, Michael addition, carbon-oxygen cleavage, and cyclization, allowing for rapid aryne vicinal difunctionalization through the installation of a benzoxazole and an olefin.²⁰⁵



Scheme 1.94: Domino synthesis of benzoxazoles from the reaction of arynes with 2-isocyanophenyloxyacrylate

1.5 OBJECTIVES AND SCOPE OF THE THESIS

Heterocyclic rings are prevalent architectural units of many pharmaceuticals which enables to interact with the biological targets. Inspired by the chemistry of heterocycles and their crucial roles in natural product synthesis, in drug discovery and in the development of new materials with various applications, we envisioned to develop novel cascade approaches for constructing diversely substituted heterocycles. Cascade reactions, which involve multiple bond-forming events in a single pot, offer powerful strategies for constructing complex organic frameworks efficiently in a controlled manner. This thesis focused on the cascade synthesis of diverse heterocycles, especially tetrahydrothiophenes, spirothiazolono-tetrahydrothiophene, α -pyrones, dihydroindoles, and benzoxazoles, aiming to expand the synthetic toolbox for accessing structurally distinct organic compounds. These molecules bearing heterocyclic cores might play crucial roles in finding lead drug molecules.

Next aim of this thesis was to identify several significant reacting partners and explore their reactivities toward the synthesis of numerous distinctive, complex, and multifunctional heterocyclic compounds. We focused on incorporating chemical diversity into the molecular framework to construct interesting compounds with a wide range of applications. The assembly of highly valuable functionalized compounds represents a highly desirable aim and challenge. Keeping these things in mind, we implemented the approaches that would involve the construction of these heterocycles with various ring sizes, substitution patterns, and functional groups, as well as the potential applications.

Today, in synthetic organic chemistry, sustainability and efficiency are the main concerns. Therefore, we envisioned to use immobilized organocatalysts/reagents to develop facile, efficient and green protocols which reduce the use of solvents, hazardous reagents and waste generation.

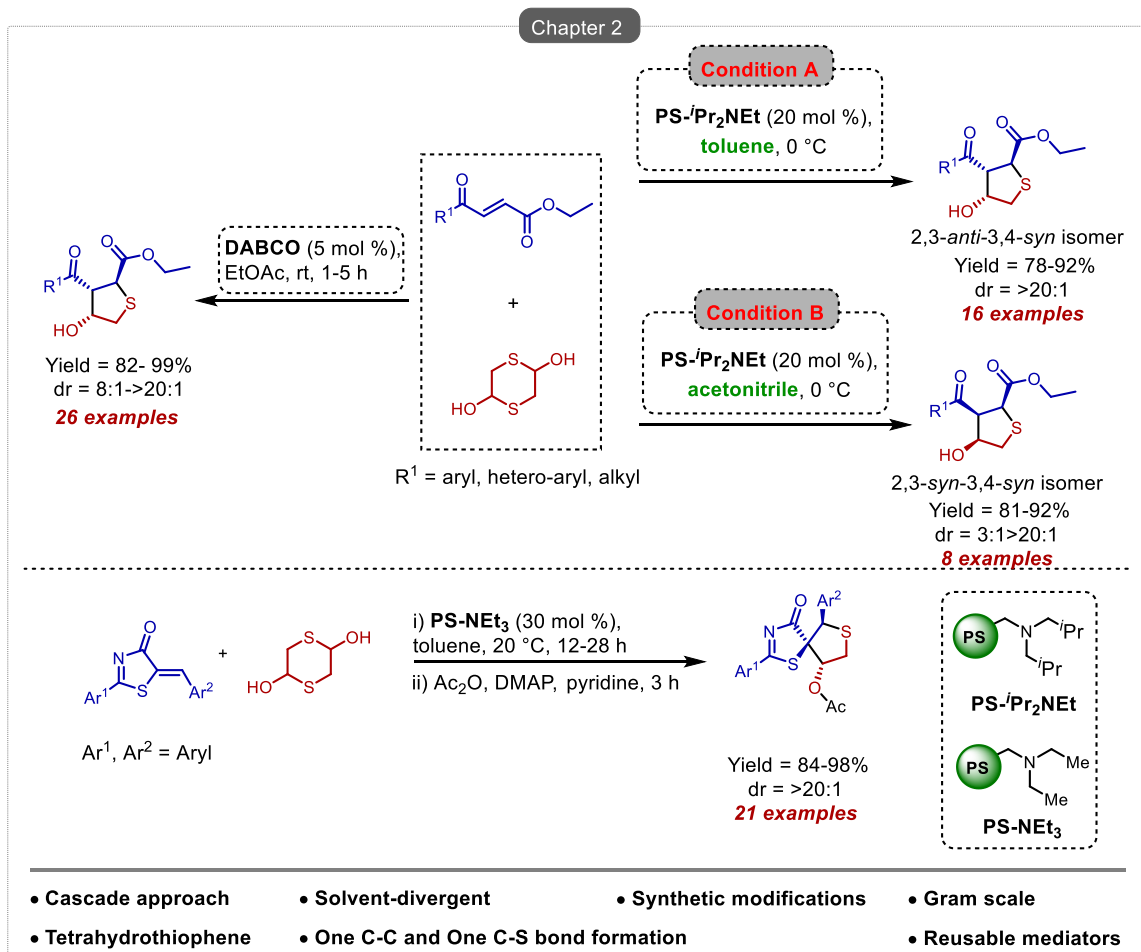
On the other hand, this research has also evaluated the scalability and practicality of the synthetic methodologies developed in this work. The efficiency of the cascade reaction would be evaluated on a gram scale to ensure the feasibility of large-scale production. Additionally, the synthetic strategy would be optimized to minimize waste, improve the overall sustainability of the process and the efficiency of immobilized organocatalysts/reagents.

Furthermore, the thesis will explore the biological activity of the synthesized heterocycles in order to identify potential lead compounds for drug discovery. The structural diversity of the synthesized heterocycles will be assessed for their ability to modulate a variety of biological targets.

1.6 STRUCTURE OF THE THESIS

To accomplish the stated objectives in the research presented in this thesis, a variety of pertinent investigations have been performed using a combination of synthesis, characterization, and applications. The thesis has been organized as follows:

Chapter 2: Stereoselective Synthesis of Tri-Substituted Tetrahydrothiophene & Spiro-Tetrahydrothiophene Via Thia-Michael/aldol Cascade Approaches

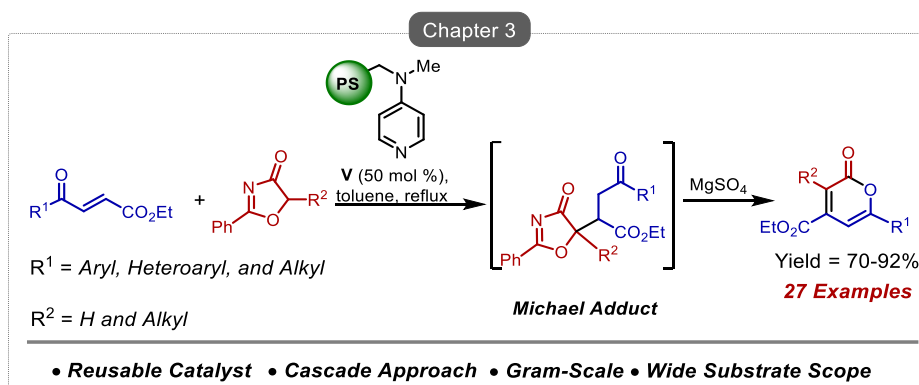


This chapter has represented several methodologies for the synthesis of tetrahydrothiophenes and spiro-tetrahydrothiophenes. This chapter was summarized in three sub-parts. Firstly, we have developed DABCO-catalyzed thia-Michael/aldol cascade reaction for constructing tri-substituted tetrahydrothiophenes. The cascade reaction has a wide range of substrate generality and excellent diastereoselectivity. Single-crystal X-ray analysis was used to determine the relative stereochemistry of the products. Further, the practical perspective and

synthetic utility of developed methodologies were demonstrated by the scale-up synthesis and transformation of products into synthetically useful compounds. As well as, an asymmetric version of the cascade reaction was also examined. Further, the binding affinity of synthesized THT derivatives were tested against MptpB proteins via in-silico docking studies. Next, to continue our research to make methodologies more versatile, sustainable, eco-friendly, and reduce purification time, we have incorporated polymer-supported catalysts/reagents. We demonstrated a polystyrene-supported amine-catalyzed solvent-controlled diastereodivergent synthesis for producing trisubstituted THTs with high yields and diastereoselectivities. The thia-Michael/aldol reaction has broad substrate generality. Gram-scale synthesis was carried out for the formation of both diastereomers, and the polymer was recovered and recycled up to ten cycles. Also, the product was transformed into a hydrogen-sulfate derivative. The relative stereochemistry of two isomers was confirmed by NOESY spectroscopy.

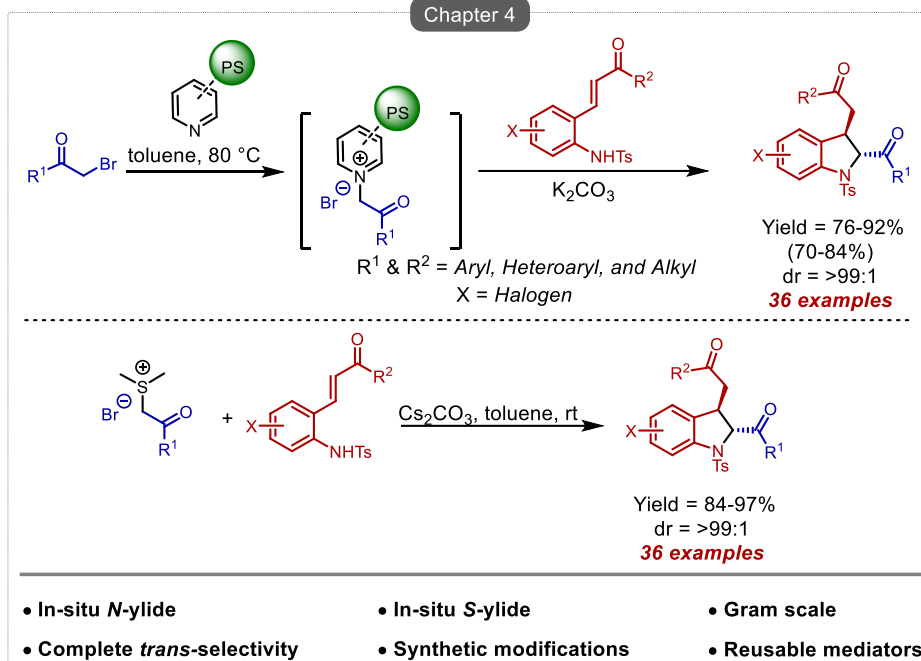
Next, we have established an efficient and sustainable approach for the synthesis of spiro-spirothiazolono-tetrahydrothiophene via thia-Michael/aldol/esterification reaction. The cascade reaction was catalyzed by a polystyrene-supported diethylaminomethyl catalyst to show a wide range of substrate scope. The relative stereochemistry of desired products was confirmed by single-crystal X-ray analysis. The reaction was found to be efficient at the gram scale, and the polymer was recovered and reused. It was found to be an effective catalyst even after twenty cycles. Furthermore, to demonstrate the synthetic utility of the developed cascade approach, the product was in-situ transformed into a hydrogen-sulfate derivative and oxidized to the corresponding 1,1-dioxide derivative. All the synthesized spirothiazolono-THTs were screened against Human Serum Albumin protein via in silico and in vitro studies. In addition, their ADME properties were also envisaged to identify plausible future therapeutic leads.

Chapter 3: Recyclable Polymer supported DMAP catalyzed One-pot Cascade Synthesis of di-/trisubstituted α -Pyrones



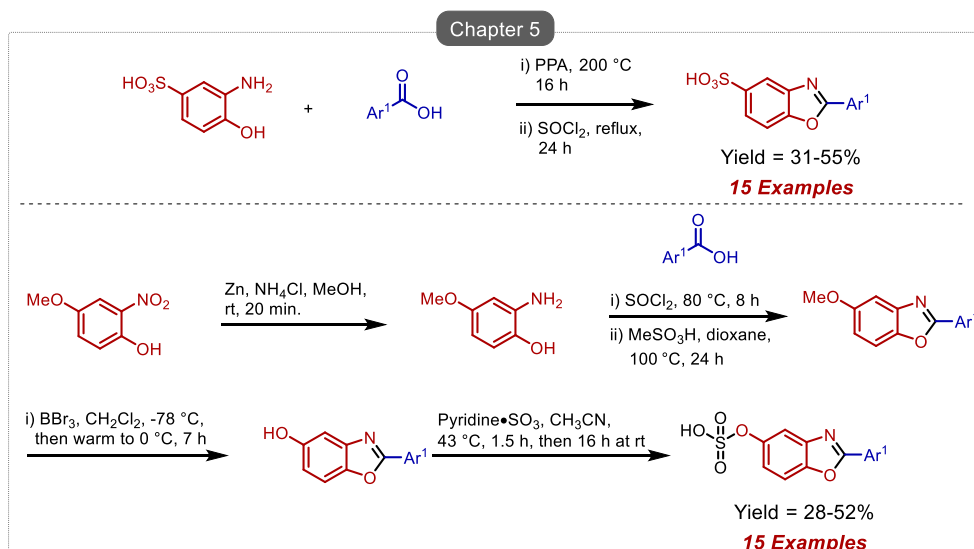
In this chapter, we have discussed the one-pot cascade reaction of α,β -unsaturated- β -ketoesters and 5H-oxazol-4-ones for the synthesis of α -pyrone derivatives. The one-pot approach involves four steps: Michael addition, ring opening, lactonization, and dehydration. A polystyrene-supported DMAP (PS-DMAP) was found to be an efficient catalyst for this cascade reaction. The reactions have a wide range of substrate tolerances. Both disubstituted and trisubstituted α -pyrones were synthesized in viable yield. Based on HRMS data from the crude mixture of unsupported DMAP-catalyzed reactions, a plausible mechanism for this one-pot cascade synthesis was proposed. To demonstrate the synthetic utility of developed methodologies, a scale-up reaction was carried out and the PS-DMAP was recovered. The recovered PS-DMAP catalyst was reused and found to be effective even after 20 cycles. In addition, the product was transformed into 1,2-diazapine derivative.

Chapter 4: Sustainable Approach for Cascade Synthesis of *trans*-2,3-Dihydroindoles Utilizing Ylide Chemistry



This chapter represents the synthesis of *trans*-2,3-disubstituted-dihydroindoles via Michael addition followed by intramolecular aza-substitution reaction. We have synthesized new and novel Merrifield resin-supported pyridines. They have been reacted with 2-bromoketones in the presence of a base to form pyridinium ylide in-situ and utilized as a C1 synthon for this tandem approach. The substrate scope was performed utilizing both supported and unsupported pyridines. The mechanism of the developed method was confirmed by HRMS analysis and the formation of *trans*-isomer as a major product was supported by DFT calculations. To represent the synthetic utility of the developed method, we have carried out the scale-up synthesis and recycling study of supported pyridines. The polymer was found to be active after ten cycles. Further, the product was transformed into synthetically useful compounds. Next, we have developed another approach for constructing dihydroindoles utilizing sulfur ylide. In-situ generated sulfur ylide undergo Michael addition/intramolecular aza-substitution reaction to afford *trans*-dihydroindoles in excellent yields and diastereoselectivities. Further, the relative stereochemistry of *trans*-isomer was confirmed by NOESY experiment and X-ray single crystal analysis.

Chapter 5: Synthesis of Benzoxazole Derivatives to Develop Molecular Agonists for Biogenesis of Utrophin



In this chapter, we have developed methodologies for the construction of benzoxazole-bearing sulfonic acid group and hydrogen-sulphate group at the 5-position. 2-arylbenzo[d]oxazole-5-sulfonic acid derivatives were synthesized in two steps, however 2-arylbenzo[d]oxazol-5-yl hydrogen sulfate derivatives were synthesized in four steps. A library of sulfonic acid or hydrogen-sulphate groups bearing several benzoxazole derivatives have been synthesized utilizing these approaches. This group of compounds seems to have a lot of promise as a potential lead molecules for the treatment of Duchenne Muscular Dystrophy Disease. We have also applied these small molecules to the delineation of structure-activity relationships with a number of potent upregulations of utrophin production to use in the treatment of Duchenne Muscular Dystrophy.

Chapter 6: Conclusions and Future Scope

The whole thesis has been summarized in this chapter with some future directions. The synthesized heterocycles might be suitable for bioactivities. We have initiated some initial testing of these derivatives in collaboration with expert groups. In future, we can further extend the scope of these cascade reactions in continuous flow technology for the development of efficient and cost-effective methodologies to produce fine chemicals. In addition, the developed protocols hold promise for the development of asymmetric variants leading to enantioenriched products. This might find industrial applications. These methodologies can be used for large-scale synthesis and also these polymers shall be useful for contentious flow synthesis of various heterocyclic compounds.