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ORGANOCATALYSIS

A GREEN TOOL FOR SUSTAINABLE DEVELOPMENTS

Edited by Bimal Krishna Banik and Bubun Banerjee

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Organocatalysis

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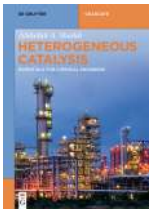

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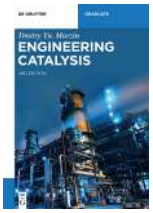

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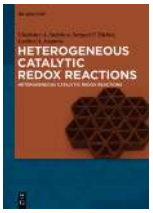

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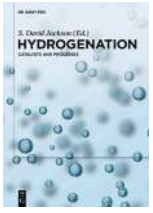

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Organocatalysis

A Green Tool for Sustainable Developments

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Dedicated to Sant Baba Iqbal Singh Ji, Founder Chancellor, Akal University

Shiromani Panth Rattan, Vidya Maartand, Padam Shri Sant Baba Iqbal Singh Ji, fondly known as 'Baba Ji', was born on May 1, 1926 in village Bharial Lahri, Tehsil Pathankot, District Gurdaspur (now Pathankot). Inspired by Sant Teja Singh Ji, the devout disciple of Sant Attar Singh Ji, he made a resolve to dedicate his life towards serving humanity and thus he started his journey of relentless service towards humanity following the footsteps of his Guru, Sant Attar Singh Ji Maharaj. He did B.Sc. in Agriculture and retired as the 'Director of Agriculture' from Himachal Pradesh Government in 1987. Realizing the poor condition, he felt to do something for the betterment of the society. With his own money he started a school called Akal Academy at Baru Sahib, Sirmaur, Himachal Pradesh, India (a prelude to Eternal University) with just five students in 1986. He tried to educate underprivileged children and treated thousands of patients at his charitable institution under The Kalgidhar Trust at Baru Sahib, Sirmaur, Himachal Pradesh, India. Baba Ji worked relentlessly in only one direction – imparting values-based education in rural India so that every rural child can have access to low-cost values-based education which is literacy embedded with moral, ethical and spiritual education. To carry forward this noble mission, he worked tirelessly and one by one, he established 129 Akal Academies in Punjab, Himachal Pradesh, Haryana, Uttar Pradesh and Rajasthan, wherein more than 70,000 students are being imparted the blend of modern scientific education. These students have not only excelled in academics but also imbibed spiritual ethos. Apart from making their life ideal and successful, they have also transformed the lives of their families and relatives who were previously addicted to consumption of various drugs. Far away from the urban milieu, these schools focus on values-based education to children from marginalized sections of society. As a social worker Baba Iqbal Singh ji didn't restricted himself just to the education sector, he was involved in every facet of community life i.e. Schools, Hospital, Colleges, Women Care Center, De-addiction Centers. Baba Ji established Akal University in 2015 which is running successfully at Talwandi Sabo in Bathinda, Punjab.

Baba ji sincerely believed that real contribution to society constitutes in working relentlessly for the poorest, oppressed and most backward sections of the society.

For his philanthropic and selfless services for social welfare, he was conferred various awards and honors:

Dedicating his entire life to the service of humanity and social welfare, Baba Ji merged with the Divine Light on 29th January, 2022 at 2.30 p.m at the age of 96.

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Preface

The organocatalysis subject has made tremendous contribution in the advancement of innovative approaches to prepare diverse molecules in chiral and achiral forms. Many scientists have placed enormous effort towards designing organocatalysts to synthesize molecules effectively. These procedures are mainly efficient, atom economical, cost-effective and environmentally benign. These processes minimize the waste accumulation and avoid the use of hazardous flammable solvents. Many reactions proceed due to catalytic activation through electrophilic and nucleophilic pathways.

This book entitled '*Organocatalysis_A green tool for sustainable developments*' has 12 chapters written by established scientists of high calibers.

In chapter 1, Ghosh *et al*. has explored the enzyme-catalyzed synthesis of numerous biologically active heterocycles. In particular, laccases, lipase, trypsin, α-amylase, Bakers' yeast have been used for various synthetic operations.

Singh and Nath have reported the use of Bronsted acidic surfactants as organocatalysts for various organic reactions in chapter 2. Some of these reactions proceed in water since surfactants can create hydrophobic opening *via* micelle formation. Under this condition, the reactants react to give the products.

In chapter 3, Kamanna *et al*. investigated natural and modified amino acids-based organocatalysts for asymmetric synthesis. L-Proline and its derivatives are explored for the asymmetric synthesis reaction. Because of the major impact of the generic modes of activation, enzymatic process has become popular.

In chapter 4, Jonnalagadda *et al*. have highlighted efforts towards designing and fusing organocatalysts to prepare chiral compounds. This chapter has given importance on enamine, iminium ion, hydrogen bonding ability, and phase transfer organocatalysts.

Pellissier has described the use of enantioselective organocatalytic domino/tandem processes in the total synthesis of medicinally active compounds in chapter 5.

Hajra *et al*. have shown zwitterionic imidazolium salt-catalyzed synthesis in chapter 6. The C2-H of the imidazole system has a significant role in catalyzing the process through electrophilic activation. An alteration of the cations and/or anions of the ionic liquids are permitted in diverse ways.

In chapter 7, Du and his group have discussed the principal progress in the application of *in situ*-generated hypervalent iodine species.

Das and Banik have focused microwave-induced enzyme-catalyzed reactions in chapter 8. Enzymes in the presence of microwave exposure become activated. These activated enzymes are able to catalyze various reactions.

In chapter 9, Banik, Sahoo and their group have explored organocatalytic methods as a tool to accelerate the synthesis of new drug molecules with superior physicochemical and pharmacological activities.

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Maddila *et al.* have highlighted the importance of organocatalytic aldol and Michael reactions in diverse solvents to construct desired molecules enantio selectively and diastereo selectively in chapter 10.

Banerjee *et al.* summarize a few organic reactions that are performed using sulfonated β-cyclodextrins such as β-cyclodextrin sulfonic acid, β-cyclodextrin propyl sulfonic acid, β-cyclodextrin butyl sulfonic acid in chapter 11.

In chapter 12, Banerjee and his group have demonstrated Baker's yeast-mediated various organic reactions. Many heterocyclic compounds are prepared employing Baker's yeast.

The editors of this book express their gratitude to all the authors for contributing such good chapters. The contribution of Ms. Stella Muller and Ms. Christene Smith has tremendous. This book will not be completed without the timely support from the authors, Ms. Muller and Ms. Smith. We hope that this book on organocatalysis will be used extensively by the scientific community. Thank you ALL.

Prof. Bimal Krishna Banik
and
Dr. Bubun Banerjee

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Bimal Krishna Banik*, Biswa Mohan Sahoo, Abhishek Tiwari, Varsha Tiwari, Adya Jain and Preetismita Borah

1 Synthetic drives for useful drug molecules through organocatalytic methods

Abstract: The treatment of various pathological conditions in human beings involves the use of safe and efficacious drug substances. But there are different complications associated with the treatment of various disease states including drug resistance, adverse drug reactions, toxicity, etc. To minimize these problems, there is an urgent need to develop new therapeutics with suitable pharmacokinetic and pharmacodynamic properties. So, the organocatalytic methods are emerged as a potential synthetic tool to accelerate the design of new drug candidates with improved physicochemical and pharmacological properties, selectivity, and efficiency for the treatment of life-threatening diseases. Organocatalytic reactions refer to the chemical reaction that is accelerated by organic catalysts instead of using organometallic catalysts. Organocatalysts are more advantageous in comparison to metallic catalysts because organocatalysts are cost-effective, stable, efficient, non-toxic, readily available, and easy to handle. In addition to this, the organocatalysis method involves an eco-friendly reaction by minimizing the formation of by-products and reducing the chemical hazards. Organocatalysts are categorized into four classes such as Lewis acids, Lewis bases, Bronsted acids, and Bronsted bases. These catalysts are generally involved in various reactions mechanisms such as Aldol reaction, Diels–Alder reactions, Michael Addition and Knoevenagal reactions, etc. The utility of organocatalyst in synthetic chemistry results in the development of medicinally active compounds with diverse structural features.

Keywords: biological activity; drugs; organocatalyst; reaction; synthesis.

1.1 Introduction

Catalysts refer to the chemical substances that promote the rate of any organic reaction without affecting its equilibrium stage [1]. It acts by decreasing the activation energy of

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the chemical process [2]. Chemical reactions proceed in the presence of catalysts by interacting with reactants that lead to the generation of the intermediate materials which further undergo reaction to produce final products [3]. Catalysts are commonly classified based on their structure, composition, types of synthesis, and state of aggregation. According to the state of aggregation, catalysts are categorized into two types including homogeneous and heterogeneous catalysts [4]. The function of homogeneous catalysts is carried out in the same phase as the reactants whereas the heterogeneous catalysts exhibit their activities in different phases than the reacting substances. Further, catalysts are categorized into different types such as organic, enzymatic, or metallic [5]. Out of these, organic catalysts or organocatalysts are more advantageous in terms of synthetic range, less toxic, economically viable, mild reaction conditions, absence of metallic substances, less polluting, robust, and stable in air and water, as shown in Table 1.1. Hence, the use of organocatalyst in the synthesis of drug molecules follows the protocols of the "green chemistry" approach [6]. Organocatalyst represents the low molecular weight organic molecule that catalyzes several organic reactions. The organocatalyst is mainly composed of C, H, N, S, and P. The structures of organocatalysts may be presented as chiral or achiral (Figures 1.1 and 1.2) [7, 8].

Considering the health-related issue, there is a continuous increase in challenges associated with the safety and effective management of infectious disorders that impact the development of potential therapeutics with appropriate pharmacokinetic and pharmacodynamic properties. So, organocatalytic methods have emerged as a green technique for the functionalization of heterocyclic compounds during drug synthesis. This method involves an environment-friendly process to perform stereoselective or asymmetric synthesis to generate new drug molecules (Figure 1.3) [9].

Organocatalysis can be applied successfully to produce medicinally active compounds *via* different synthetic approaches including secondary amine catalysis *via*

Table 1.1: Advantages and limitations of organocatalyst.

Advantages	Limitations
Less toxic	High catalyst loading
Economic	Difficult in the separation of catalyst from the product
Stable in oxygen and water	Chemical reactions are carried out in a dilute solution
Less pollution	Large quantity of waste materials
No contamination of metallic substances	Corrosion of reactor
Mild reaction conditions	Difficult in separation
Easy preparation	Reaction mechanisms unknown
Easily available	Nonselective to chiral catalysis
Easy scale-up	Long reaction time

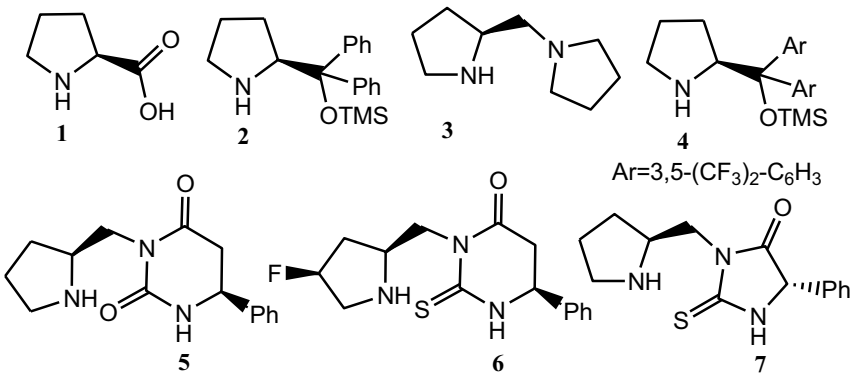


Figure 1.1: Chiral organocatalysts: proline (**1**) and derivatives (**2**–**4**), pyrimidones (**5**–**6**), and imidazolidone (**7**).

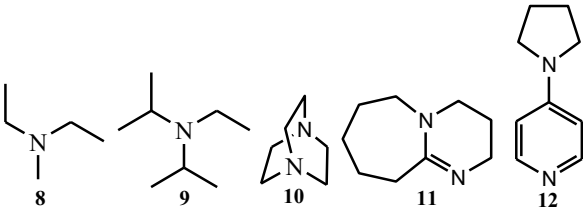


Figure 1.2: Non-chiral organocatalysts TEA (**8**), DIPEA (**9**), DABCO (**10**), DBU (**11**), PPY (**12**).

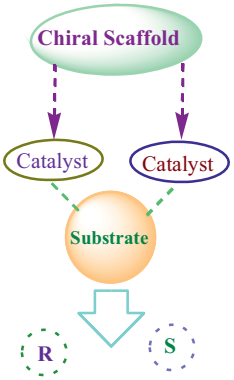


Figure 1.3: Stereoselective reaction via organocatalysis.

enamines, secondary amine catalysis *via* iminium ions, phase transfer catalysis (PTC), nucleophilic catalysis, hydrogen bonding catalysis, Bronsted base catalysis, Lewis acid, and Lewis bases catalysis as depicted in Figure 1.4 [10].

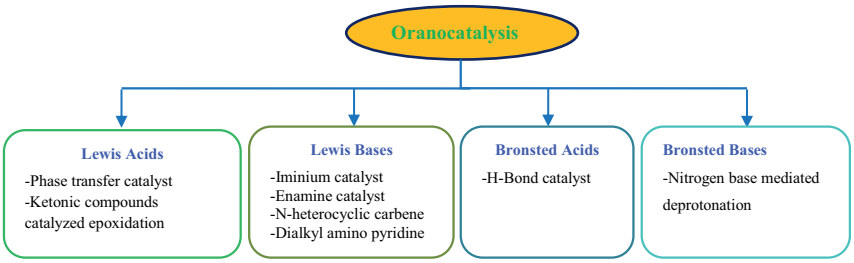


Figure 1.4: Types of organocatalysis.

1.2 Organocatalytic methods in chemical reactions

Organocatalysts are involved in different chemical reactions including Michael-reactions, Diels–Alder reactions, cycloaddition reactions, Knoevenagel condensation, Heck reaction, Mannich reactions, Aldol condensation, and halogenations, etc. as presented in Table 1.2 and Figure 1.5 [11].

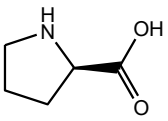
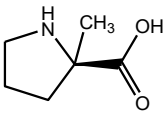
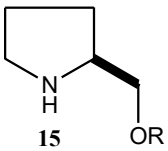
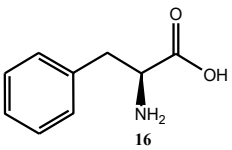
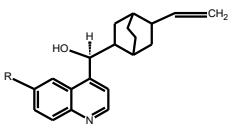
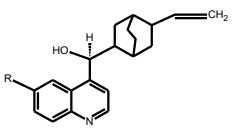
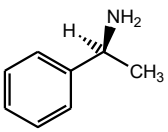
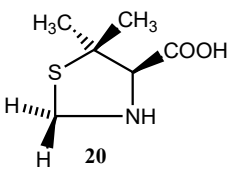
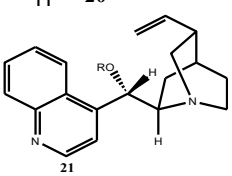
1.2.1 Organocatalysts in Michael reactions

Michael addition reaction is considered as a suitable methods in synthesis of organic compounds for the production of carbon–carbon (C–C) bonds. This reaction involves the nucleophilic addition of carbanion or nucleophile to the α,β-unsaturated carbonyl compound containing electron-withdrawing group. Michael addition reaction is thermodynamically controlled (Figure 1.6). Organocatalytic Michael reactions were developed during 2009 [12].

The compound containing active methylenes group (malonates and nitroalkanes) are called Michael donors whereas the Michael acceptors are activated olefins such as α,β-unsaturated carbonyl compounds as presented in Table 1.3 [13].

P-BEMP (**36**) is used as an efficient user-friendly and recyclable heterogeneous organocatalyst for the Michael addition reaction of 1,3-dicarbonyl compounds. P-BEMP is chemically *N*-phenyl-tris(di-methylamino)iminophosphorane immobilized with polystyrene resin (Figure 1.7). In this chemical reaction, the anhydrous solvents or an inert atmosphere is not required and it proceeds smoothly at room temperature [14].

Table 1.2: Role of organocatalysts in chemical synthesis.

Organocatalysts	Structure	Chemical reactions
L-proline (**13**)	 **13**	Intermolecular Michael addition Aldol reaction Mannich reaction
α-methyl-L-proline	 **14**	Intra-molecular α-alkylation of aldehydes
L-proline-derived amino ethers	 **15**	Mannich reaction
L-Phenylalanine	 **16**	Intra-molecular Aldol reaction
Quinine R = –OCH_3 (–) 8*S*: 9*R* isomer Quinidine R = –OCH_3 (+) 8*R*: 9*S* isomer	 **17**	Halogenation of carbonyl compounds Diels–Alder reaction
(–)-Cinchonidine R = –H	 **18**	Synthesis of β-Lactam from imines and ketenes Diels–Alder reaction Intra-molecular Michael addition
(*S*)-1-phenylethanamine	 **19**	Intra-molecular Michael addition
(*R*)-5,5-dimethyl-thiazolidine-4-carboxylic acid	 **20**	Mannich reaction Intermolecular Aldol reaction
(+)-Cinchonine, R = H	 **21**	Inter-molecular Michael addition Diels–Alder reaction Synthesis of β-Lactam from imines and ketenes Synthesis β-Lactone from aldehydes and ketenes

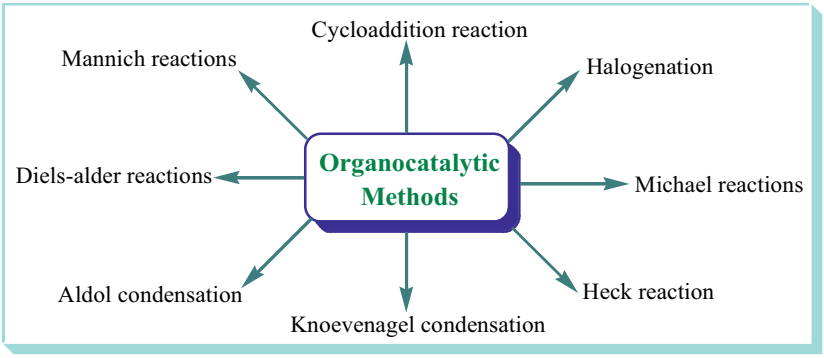


Figure 1.5: Organocatalytic methods in chemical reactions.

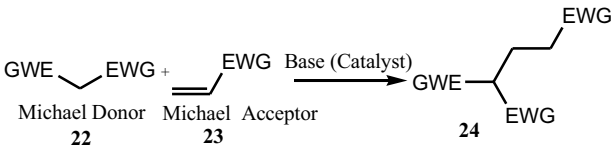
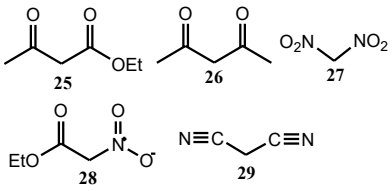
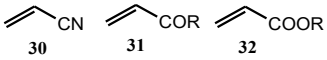


Figure 1.6: Organocatalysts in Michael reactions.

Table 1.3: List of Michael donors and acceptors.

Donors	Acceptors
	

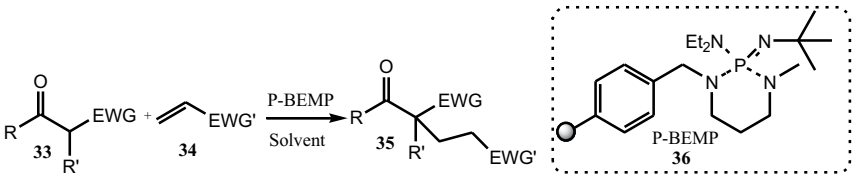


Figure 1.7: Use of P-BEMP as heterogeneous organocatalyst for the Michael addition.

1.2.2 Organocatalysts in Diels–Alder reactions

Diels–Alder reaction involves the chemical reaction between diene (**37**) and dienophile (**38**) to produce a corresponding cyclohexene derivative (**39**) (Figure 1.8). Generally, substituted alkenes are termed as dienophile [15].

MacMillan et al. reported the highly enantioselective organocatalytic Diels–Alder reaction (Figure 1.9). The organo-catalyzed Diels–Alder reaction involves addition reaction between Cinnamaldehyde (**40**) and Cyclopentadiene (**41**) to afford two racemic diastereo-isomers *endo* and *exo*-product. Out of which, the *endo*-isomer (**42**) is more predominate [16].

1.2.3 Organocatalysts in Knoevenagel condensation

Knoevenagel condensation is a nucleophilic addition reaction that involves the reaction between active methylene compounds (**45**) and aromatic carbonyl compounds containing aldehyde or ketonic group (**44**) to produce corresponding α,β-unsaturated compounds (**46**) (Figure 1.10) [17].

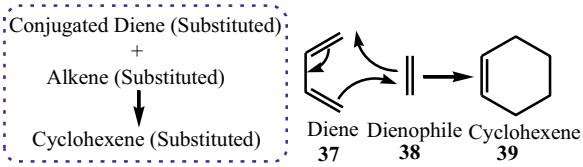


Figure 1.8: Diels–Alder reaction.

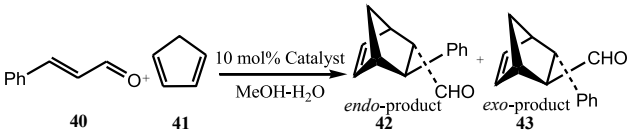


Figure 1.9: Enantioselective organocatalytic Diels–Alder reaction.

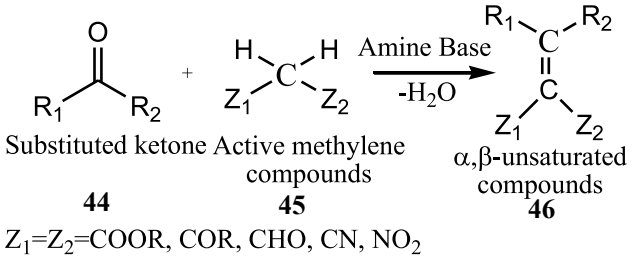


Figure 1.10: Knoevenagel condensation.

Arylaldehyde (**47**) undergoes reaction with acetylacetone (**48**) in the presence of piperidine produces 3-benzylidenepntane-2,4-dione (**49**) *via* Knoevenagel condensation reaction (Figures 1.11 and 1.12).

Das et al. reported the reaction between active methylene compounds (**53**) and aromatic carbonyl compounds (**54**) *via* Knoevenagel condensation by using quinine (**56**) as an organocatalyst under solvent-free conditions to produce the corresponding alkenes (**55**) with an excellent yield up to 90% (Figure 1.13). The chemical reaction proceeds under solvent-free conditions in the presence of a catalytic amount of quinine (15 mol %) at room temperature. It follows a green approach in which the organocatalyst was recovered and recycled without considerable loss of catalytic activity [18].

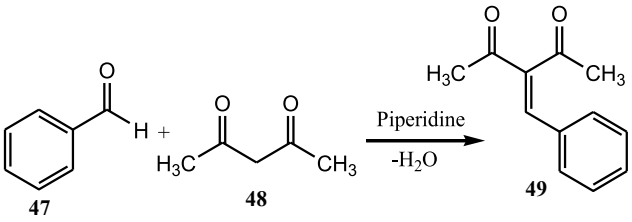


Figure 1.11: Synthesis of 3-benzylidenepntane-2,4-dione.

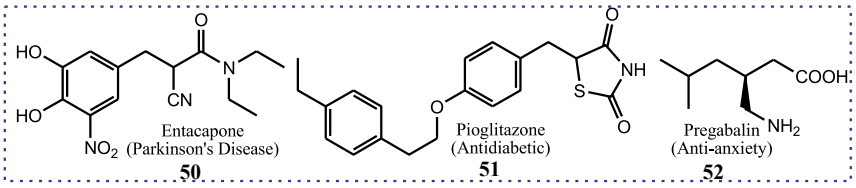


Figure 1.12: List of drugs derived through Knoevenagel condensation.

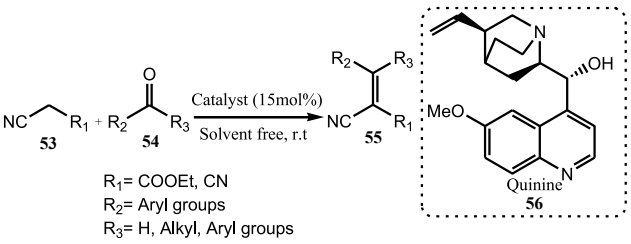


Figure 1.13: Knoevenagel condensation using quinine as organocatalyst.

1.2.4 Organocatalysts in Mannich reactions

Mannich reaction involves the formation of iminium ions from ammonia or amine (**58**) (primary or secondary) and formaldehyde (**59**). The final product formed during the Mannich reaction is known as a Mannich base (β-amino-carbonyl compound). Rolitetracycline is the N-Mannich base pro-drug that is prepared from the antibiotic tetracycline by condensation with pyrrolidine and formaldehyde (Figure 1.14) [19].

Dimethylamine (**61**) reacts with cyclohexanone (**62**) in the presence of formaldehyde (**63**) produces 2-((dimethylamino)methyl)cyclohexanone *via* Mannich reaction (Figure 1.15) [20].

Pan et al. reported the organocatalytic asymmetric synthesis of 3,3-disubstituted-3,4-dihydro-2-quinolones (**67**) *via* Mannich reaction (Figure 1.16). The bifunctional

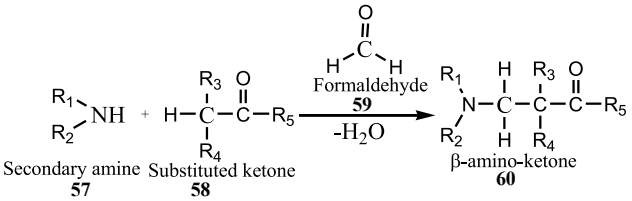


Figure 1.14: Mannich reaction.

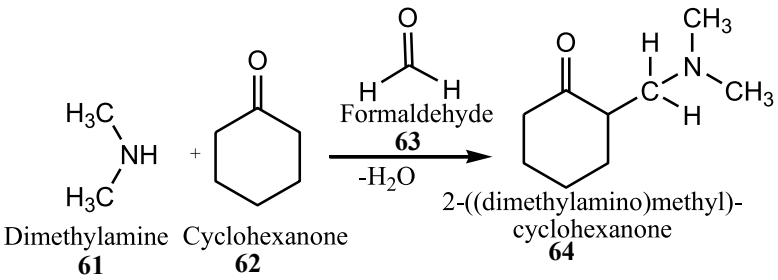


Figure 1.15: Synthesis of 2-((dimethylamino)methyl)cyclohexanone via Mannich reaction.

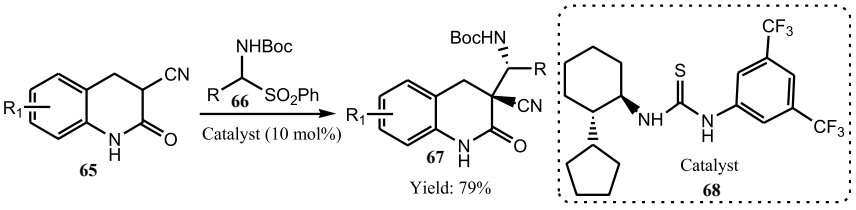


Figure 1.16: Synthesis of quinolones *via* organocatalytic Mannich reaction.

amino-thiourea catalysts (**68**) derived cyclohexyldiamine were utilized to afford the final products with high enantio- and diastereomeric selectivity [21].

1.2.5 Organocatalysts in Aldol condensation

Aldol condensation involves the reaction between enol or enolate ion and carbonyl compound to produce β-hydroxy carbonyl compounds containing aldehyde or ketonic group followed by dehydration to yield conjugated enone (**71**) (Figure 1.17). This condensations reaction is utilized to generate new carbon–carbon (C–C) bonds [22].

Chiral amino acids like L-proline and its derivatives are used as organocatalysts in an Aldol reaction to produce high yields of products with high stereo-selectivity. Yolacan et al. reported the asymmetric Aldol reaction in the presence of Pro-Phe derivatives as organocatalysts (Figure 1.18). The reaction was performed between aliphatic ketonic compounds (**75**) and various aromatic aldehydes (**76**) in water [23].

1.2.6 Organocatalysts in halogenations

Halogenation reaction involves the introduction of one or more halogens into a compound by replacing a hydrogen atom of that compound (Figure 1.19). Chlorine and bromine can be added to the aromatic group (**79**) through the use of Cl_2 and Br_2 in the

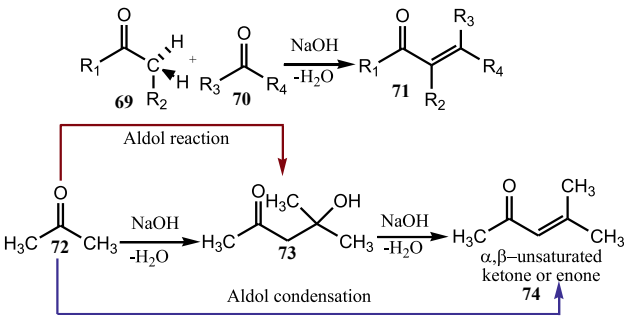


Figure 1.17: Aldol condensation.

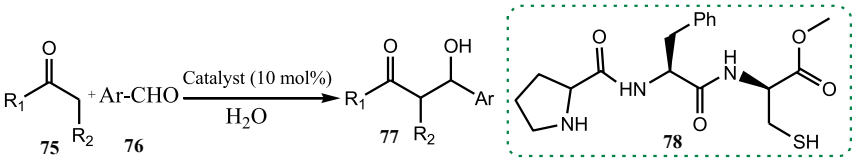


Figure 1.18: Asymmetric Aldol reaction via organocatalysts.

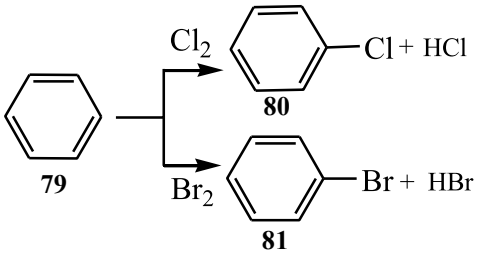


Figure 1.19: Halogenation reaction.

presence of an appropriate Lewis acid catalyst [24]. These chemical reactions proceed through the following steps.

1. Activation of electrophile by Lewis acid.
2. Attack of activated electrophile by benzene.
3. Deprotonation to restore the aromatic ring.

A protocol was developed for the enantioselective organocatalytic halogenation (e.g., chlorination) of cyclic and acyclic β-keto esters (**82**) and cyclic β-diketones (**83**). It is also applied for the asymmetric bromination of β-keto esters (Figure 1.20). This method utilizes benzoylquinidine as organocatalyst and polyhalogenated quinolinones as the source of the halogen [25].

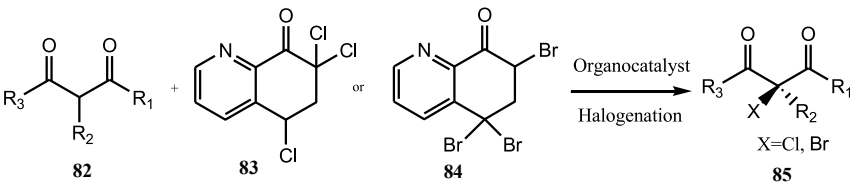


Figure 1.20: Enantioselective organocatalytic chlorination.

1.2.7 Organocatalysts in Paal–Knorr pyrrole synthesis

Darabi et al. demonstrated the metal-free catalytic eco-friendly technique for the Paal–Knorr pyrrole synthesis (Figure 1.21). It involves the reaction of hexane-2,5-dione (**86**)

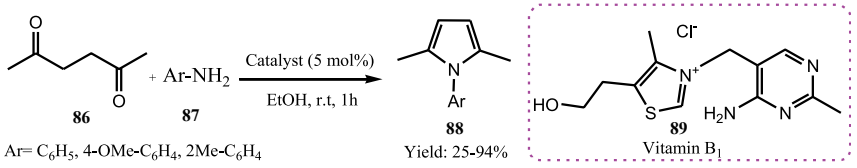


Figure 1.21: Vitamin B_1-catalyzed synthesis of substituted pyrroles.

with different substituted aromatic amines (**87**) in ethanol at room temperature for 1 h in the presence of vitamin B_1 (**89**) as an organocatalyst to produce the corresponding *N*-substituted pyrroles (**88**) with moderate to excellent yield (25–94%). Vitamin B_1 has used an organocatalyst and the structure of vitamin B_1 comprises the pyrimidine ring and a thiazole ring linked by the methylene bridge. Vitamin B_1 is considered as a non-toxic green organocatalyst. It is soluble in water, inexpensive, and non-flammable [26, 27].

Bhandari et al. performed the synthesis of a series of *N*-substituted 2,5-dimethylpyrroles (**92**) *via* Paal–Knorr cyclo-condensation. It involves a two-component reaction of hexane 2,5-dione (**90**) with different aromatic hydrazides (**91**) in methanol catalyzed by saccharin at room temperature for 30 min (Figure 1.22). This technique is more advantageous in terms of non-toxicity, low cost, ecological safety, easy isolation of the product, and reusability of the catalyst that could apply to a wide-ranging substrate scope in good to excellent yield [28].

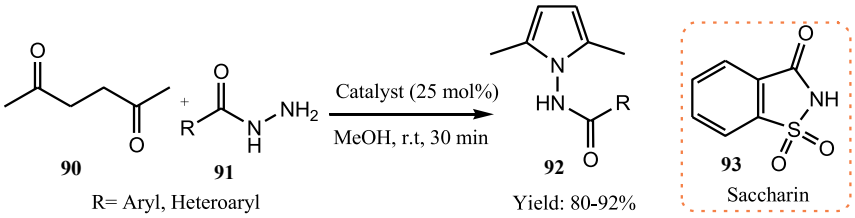


Figure 1.22: Saccharin-catalyzed synthesis of pyrroles.

Aghapoor et al. reported the organocatalytic synthesis of *N*-substituted pyrroles (**96**). It involves the reaction of hexane-2,5-dione (**94**) with different aromatic amines (**95**) in the presence of the natural primary amino acid *l*-tryptophan (**97**) as an organocatalyst at 70 °C under the solvent-free condition to obtain the corresponding product with 86–97% yield in 1–2 h (Figure 1.23) [29].

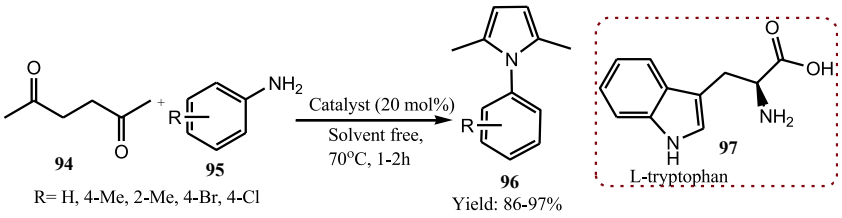


Figure 1.23: Synthesis of pyrroles *via* double-condensation reaction.

Azizi et al. reported the organocatalytic route for the synthesis of *N*-substituted pyrroles (**100**) with a yield of 85–97%. It involves the reaction of tetrahydro-2,5-dimethoxyfuran (**98**) with different arylamines (**99**) in the presence of anilinium squarate salt as an organocatalyst in the aqueous medium at 60 °C for 3–6 h (Figure 1.24).

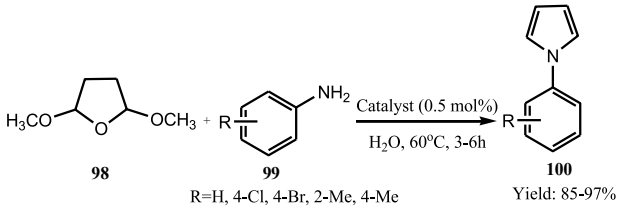


Figure 1.24: Preparation of *N*-substituted pyrroles from tetrahydro-2,5-dimethoxyfuran and amines.

Anilinium squarate salt is produced by the reversible acid-base treatment of aniline with squaric acid [30].

1.3 Organocatalytic methods in drug synthesis

Cinnamic acids (**103**) are used as intermediates for the synthesis of biologically active compounds (Figure 1.25). So, cinnamic acids are produced via Knoevenagel condensation of aromatic aldehydes (**101**) and malonic acid (**102**) in the presence of an organocatalyst [31].

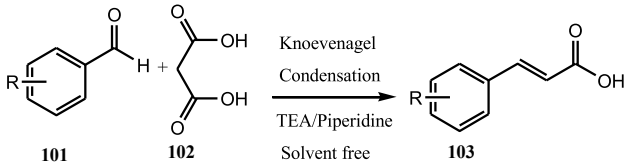


Figure 1.25: Reaction scheme for the synthesis of cinnamic acid.

Salycylaldehyde (**104**) reacts with diethyl malonate (**105**) in the presence of piperidine produces ethyl coumarin-3-carboxylate (**106**) (Figure 1.26) [32]. Here, piperidine acts as an organocatalyst.

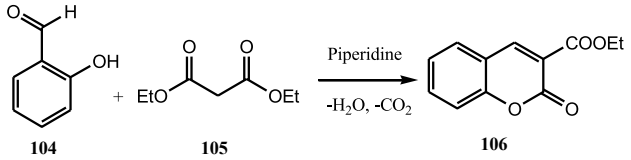


Figure 1.26: Synthesis of ethyl coumarin-3-carboxylate.

The Knoevenagel condensation is the key step for the synthesis of antimalarial drug-like lumefantrine (Figure 1.27). Lumefantrine (**108**) is the class of fluorenes type. It is chemically called 9-(*p*-chlorobenzylidene)-9H-fluorene that is substituted with

chloro group and by 2-(dibutyl amino)-1-hydroxyethyl group at positions C_2, C_7, and C_4 respectively [33].

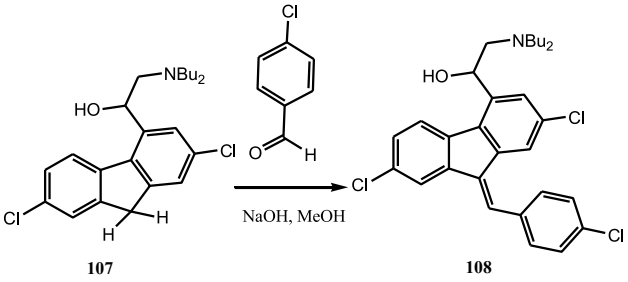


Figure 1.27: Synthesis of lumefantrine.

Alves et al. performed the organocatalytic synthesis of 7-chloroquinoline-1,2,3-triazoyl carboxamides (**111**) and evaluated as potential antinociceptive, anti-inflammatory, and anticonvulsant agents (Figure 1.28). It involves the reaction between 4-azido-7-chloroquinoline (**109**) and *β*-oxo-amides (**110**) in presence of the pyrrolidine (5 mol %) as organocatalyst [34].

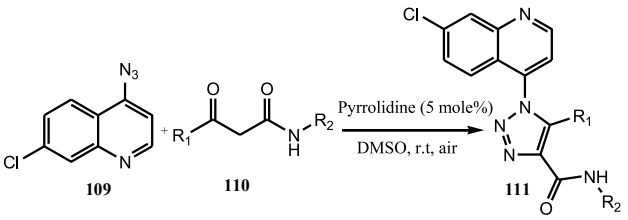
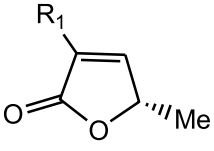


Figure 1.28: Organocatalytic synthesis of 7-chloroquinoline-1,2,3-triazoyl carboxamides.

The compound butenolide is chemically known as 3-alkyl-5-methyl-2[5*H*]furanone. It is used as the synthon to produce medicinally active compounds via a sequential organocatalytic one-pot approach (Figure 1.29). Butenolide (**112**) acts as mosquito larvicidal. Butenolide A is present as a constituent in mushroom flavor whereas Butenolide B exhibits the fungicidal property. The polyketide metabolites include various functionalized butenolides such as (–)-blastmycinolactol K, (+)-blastmycinone L, (–)-NFX-2 M, and (+)-antimycinone N. These compounds exhibit



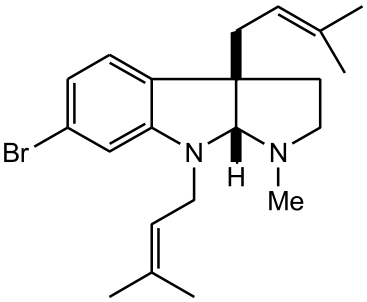
112

A: R_1=CH_3; B: R_1=CH_2CH_3
C: R_1=C_4H_9; D: R_1=C_6H_{13}

Figure 1.29: Structure of butenolides.

the antifungal and antitumor activities. Similarly, Butenolide S and T are reported as mosquito larvicides [35].

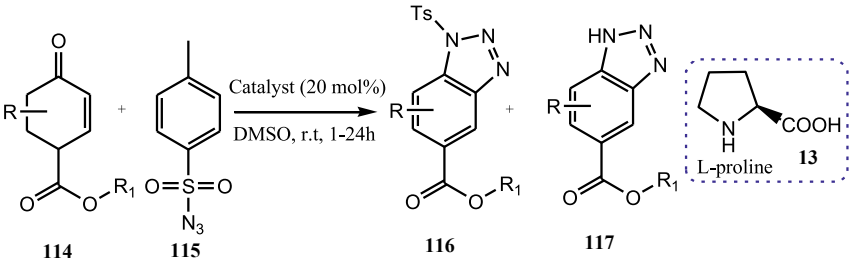
Flustramines A and B are found to block voltage stimulated potassium channel and demonstrated both skeletal and smooth muscle relaxant properties. The synthesis of flustramine B (**113**) is carried out through the enantioselective organocatalytic method (Figure 1.30) [36].



113

Figure 1.30: Structure of flustramines B.

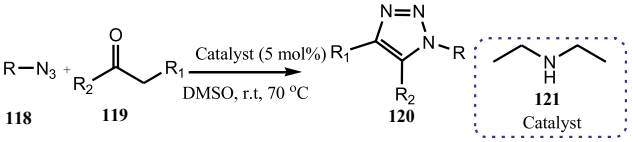
Ramachary et al. developed the synthesis of 1,2,3-triazole derivatives (**116**) *via* enamine mediated [3 + 2]-cycloaddition reaction, catalyzed by L-proline (Figure 1.31) [37]. The chiral structure of L-proline enables the enantioselective synthesis of specific enantiomers or diastereomers.



114 **115** **116** **117**

Figure 1.31: Synthetic route for 1,2,3-triazoles.

Wang et al. demonstrated the regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles (**120**) during 2011. The synthesis was performed by using an organocatalytic enamine azide reaction (Figure 1.32) [38].



118 **119** **120**

Figure 1.32: Regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.

Ramachary et al. performed the organocatalytic [3 + 2]-cycloaddition reaction of substituted ketonic compounds (**123**) with azides (**122**) to produce substituted 1,2,3-triazoles (**124**) (Figure 1.33) [39].

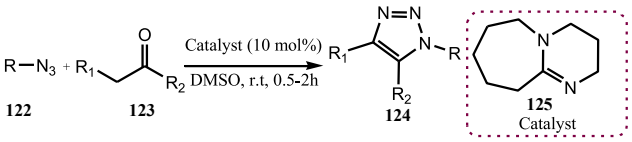


Figure 1.33: Organocatalytic method for preparation of 1,2,3-triazole derivatives.

The organocatalytic approach is utilized for synthesis of bifunctional hybrids that comprise 1,2,3-triazoyl-carboxylates and 7-chloroquinoline (**129**) (Figure 1.34). These compounds were synthesized in moderate to excellent yields (Table 1.4) *via* enamide-azide cycloaddition reaction of 4-azido-7-chloroquinoline (**126**) with a range of *β*-keto-esters (**127**) in the presence of pyrrolidine (**128**, 10 mol %) as organocatalyst. The *in vitro* antioxidant activity was carried out for the synthesized compounds including ethyl 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate and ethyl 1-(7-chloroquinolin-4-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate. The screening results revealed that the first compound is found to reduce the lipid peroxidation levels induced by sodium nitroprusside in the mice liver, whereas the second one displays the nitric oxide scavenging property [40].

Pansare et al. developed the enantioselective organocatalytic method for synthesis of 4-arylquinolizidin-2-ones. It acts as an important intermediate for the synthesis of various biomimetic alkaloids such as Lythraceae (Figure 1.35). This method involves the *S*-proline-mediated Mannich/aza-Michael reactions of arylideneacetones and Δ^1-piperideine. The total syntheses were achieved for (–)-lasubine II (**132**) and (+)-subcosine II as well as the structurally related Lythraceae alkaloids. In Mannich/aza-Michael reaction, the use of Δ^1-pyrroline provides enantiomerically enriched

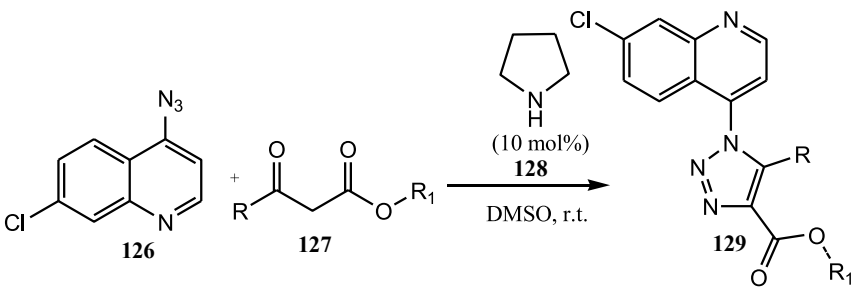


Figure 1.34: Organocatalytic synthetic approach for of 1-(7-chloroquinolin-4-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate.

Table 1.4: Optimization study of the reaction conditions.

Catalyst	mol %	Temperature (°C)	Isolated yield (%)
Et_2NH	10	70	78
L-proline	10	70	57
Pyrrolidine	10	70	93
Piperidine	10	70	57
Et_3N	10	70	68
Pyrrolidine	10	rt	90

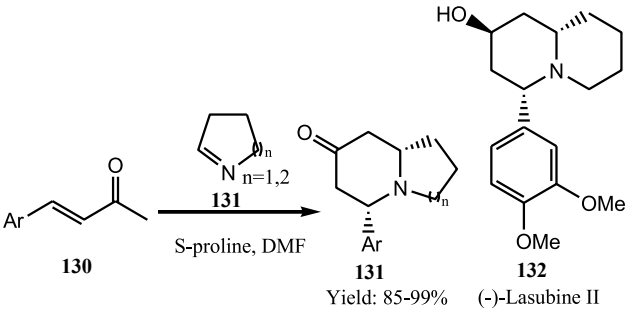


Figure 1.35: Organocatalytic synthesis of 4-arylquinolizidin-2-ones.

5-arylindolizidin-7-ones that act as precursors to non-opiate anti-nociceptive agents [41].

The organocatalytic intra-molecular aza-Michael reaction (IMAMR) is utilized as an enantioselective approach to produce different heterocyclic compounds such as indolines, isoindolines, tetrahydroquinolines, and tetrahydroisoquinolines from *o*-substituted alkylidenes, anilines, and benzylamines (Figure 1.36). This organocatalytic method is utilized for the production of the natural product such as (+)-Angustureine [42].

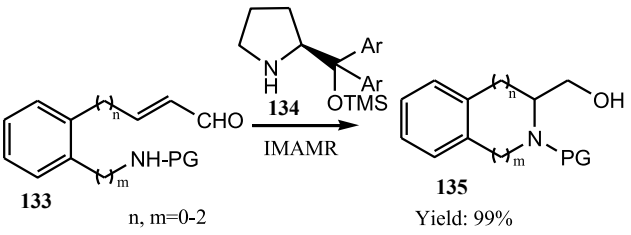


Figure 1.36: Synthesis of the natural product (+)-Angustureine.

Coumarins are the phenolic compounds that occur naturally as plant constituents. These compounds possess diverse biological activities such as antibacterial, antifungal, anticoagulant, antiviral, anticancer, and anti-inflammatory, etc. So, the coumarin derivatives are synthesized via an asymmetric organocatalytic method. Examples of coumarin-derived drugs include warfarin **136** (anticoagulant), methoxsalen **137** (treatment of psoriasis, eczema, vitiligo), and tioclomarol **138** (anticoagulant) (Figures 1.37 and 1.38) [43].

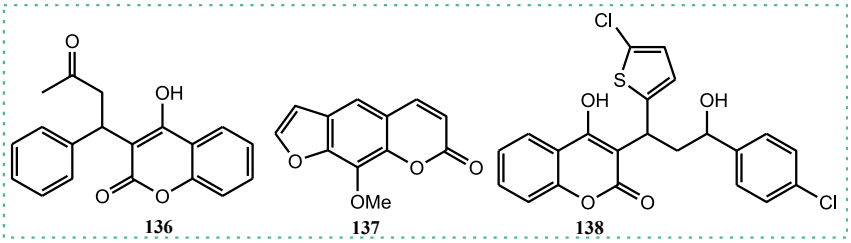


Figure 1.37: Coumarin-derived clinically available drugs.

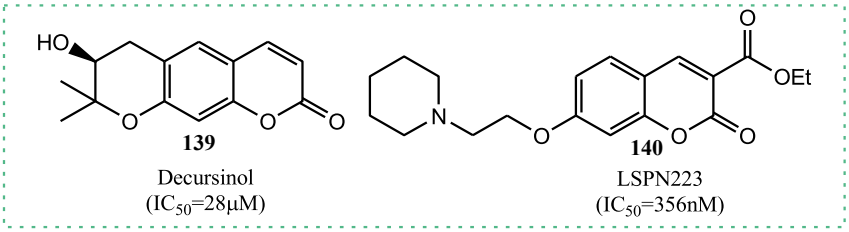


Figure 1.38: Coumarin derivatives with acetylcholinesterase inhibitory activity.

Jorgensen et al. reported the first organocatalytic asymmetric Michael addition of cyclic1,3-dicarbonyl compounds including 4-hydroxycoumarins (**141**) to α,β-unsaturated enones (**142**) (Figure 1.39). This Michael reaction is involved to produce (*S*)-warfarin (**143**) with high yields and good enantiomeric excess by using (4*S*, 5*S*)-4,5-diphenylimidazolidine-2-carboxylic acid (**144**) as organocatalyst [44].

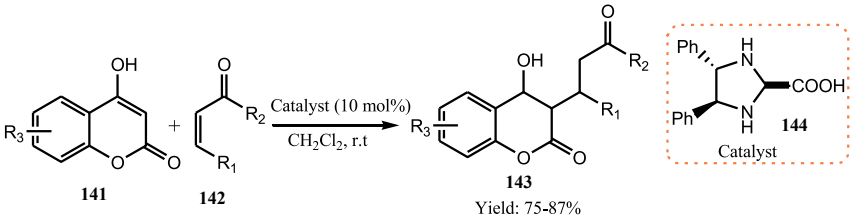


Figure 1.39: Synthesis of (*S*)-warfarin *via* organocatalytic asymmetric Michael addition reaction.

Malakar et al. demonstrated an efficient and cost-effective protocol for the synthesis of quinazolines (**147**) by using niacin (Vitamin-B_3) as a potent organocatalyst and nitriles as a C-N source (Figure 1.40). It involves the organocatalytic reaction between 2-aminobenzylamine (**145**) and a benzonitrile (**146**) to produces 2-phenylquinazoline [45].

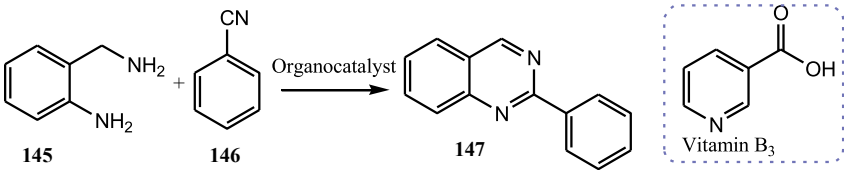


Figure 1.40: Synthesis of quinazolines by using niacin (Vitamin-B_3).

Naicker et al. reported the synthetic route for generating novel minocycline derivatives (**151**) *via* proline-catalyzed three-component Mannich reaction (Figure 1.41, Table 1.5). The Mannich adducts were screened for their *in-vitro* antibacterial activity against both Gram-negative (*Escherichia coli*: MIC 0.25 μg mL^{-1}) and Gram-positive bacteria (*Staphylococcus aureus:* MIC 0.25 μg mL^{-1}, *Bacillus subtilis*: MIC 0.06 μg mL^{-1}) [46].

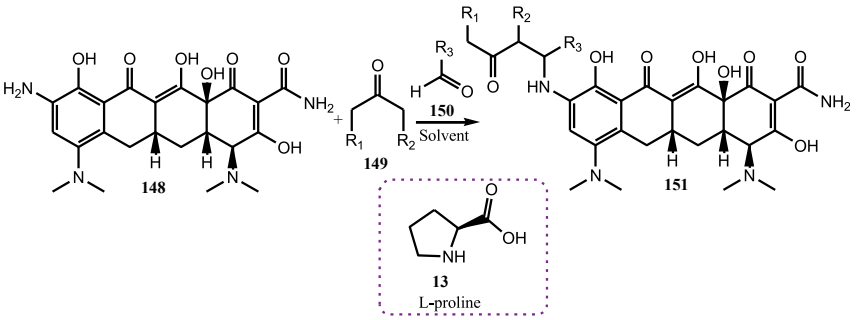


Figure 1.41: Preparation of minocycline derivatives *via* a three-component Mannich reaction.

Table 1.5: Optimization of reaction condition for three-component Mannich reaction.

Entry	Solvent	Catalyst	Mole %	Yield (%)
1	DMSO	L-proline	30	41
2	DMF	L-proline	30	57
3	Ethanol	L-proline	30	82
4	Methanol	L-proline	30	96
5	Methanol	Pyrrolidine	30	84

Compounds like 4*H*-pyran and 1,4-dihydropyridines derivatives are the promising scaffolds present in the structures of different medicinally active compounds. Dihydropyridines derivatives are significant moieties that exhibit antibacterial, analgesic, and fungicidal activities whereas 4*H*-pyran-containing compounds display antibacterial and anti-cancer activities (Figure 1.42). So, the organocatalytic methods are used to generate hybrid compounds of 1,4-dihydropyridines and 4*H*-pyran under optimized conditions. These compounds were screened for their cytotoxic activity against different cancer cell lines such as KB and HepG2 [47, 48].

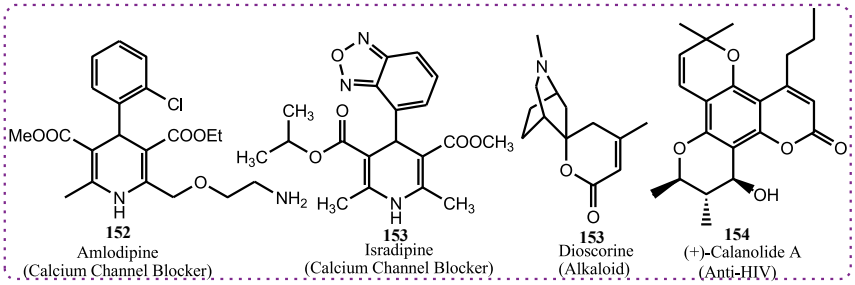


Figure 1.42: Chemical structures of pyran and dihydropyridine derivatives with bioactivity.

The hybrid 4*H*-pyrano[2,3-*b*]pyridine derivatives (**157**) are synthesized by the reaction between 1,4-dihydropyridines (**155**) and acrolein (**156**) in the presence of (5*S*)-(−)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone monohydrochloride as an organocatalyst (**158**) (Figure 1.43) [49].

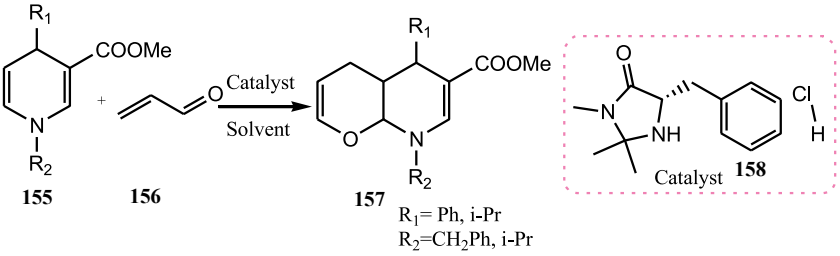


Figure 1.43: Synthesis of enaminoesters, 1,4-dihydrpopyridine, and 4*H*-pyrano[2,3-b]pyridine.

Enders et al. reported the asymmetric organocatalytic method for the stereoselective synthesis of 4-aminoisochromanones (**161**) via a direct one-pot intramolecular Mannich reaction (Figures 1.44 and 1.45). It involves the reaction between 2-oxopropyl-2-formylbenzoates (**159**) and anilines (**160**) in the presence of secondary amine as catalyst [50].

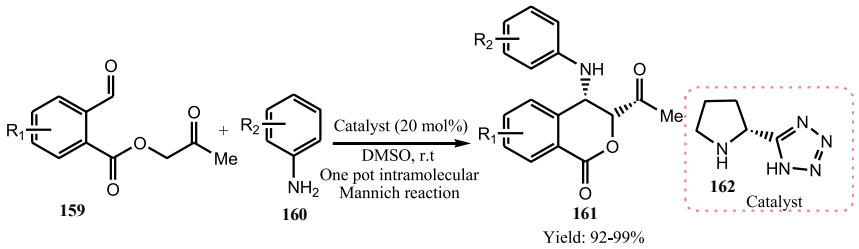


Figure 1.44: Organocatalytic method for the synthesis of 4-aminoisochromanones.

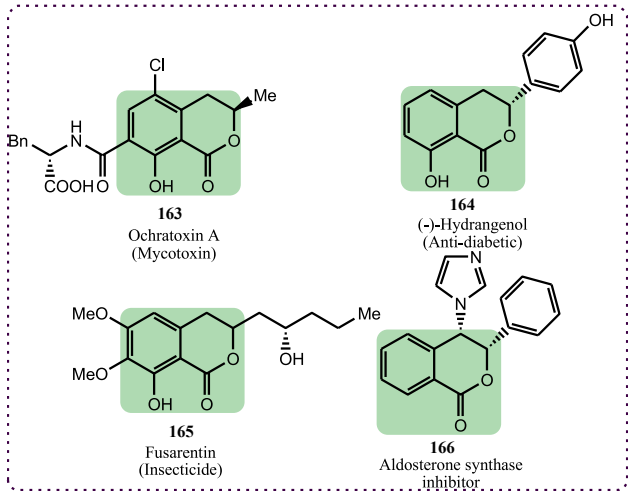


Figure 1.45: Biological activities of natural 3,4-disubstituted isochromanones.

Wang et al. demonstrated the synthesis of 4-substituted 3,4-dihydrocoumarins (**169**) via an organocatalytic double decarboxylation method (Figure 1.46, Table 1.6). 3,4-dihydrocoumarin scaffold is considered an important building block that exhibits diverse bio-activities including aldose reductase inhibitor, and anti-herpetic, etc. (Figure 1.47) [51].

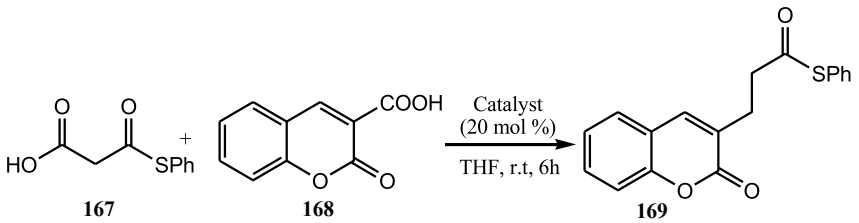


Figure 1.46: Synthesis of 4-substituted 3,4-dihydrocoumarins via an organocatalyst.

Table 1.6: Optimization study on effect of organocatalyst on synthesis of coumarins.

Entry	Catalyst	Yield (%)
1	Pyrrolidine	44
2	TEA	56
3	DIPEA	41
4	N-methyl morpholine	66
5	DMAP	49

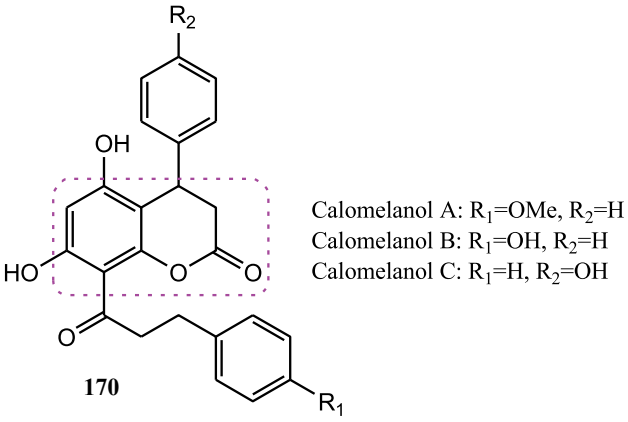


Figure 1.47: Structures of 4-substituted 3,4-dihydrocoumarin scaffold.

Alves et al. performed the organocatalytic method for the synthesis of 1,2,3-triazoyl-zidovudine derivatives (**173**) (Figure 1.48) and evaluated their antioxidant

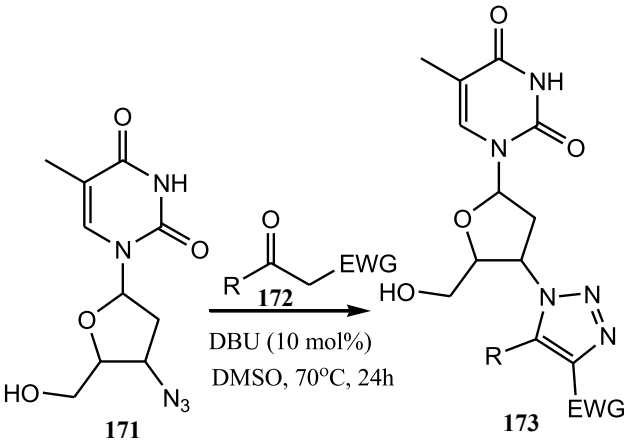


Figure 1.48: Synthesis of 1,2,3-triazoyl-zidovudine derivatives via DBU.

property. These hybrid compounds were synthesized in excellent yields (Table 1.7) by reacting zidovudine (**171**) with different keto compounds, such as β-diketones, β-keto-amides, β-keto-esters, α-keto-nitriles, and β-keto-sulfones in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as organocatalyst. The screening results reported that some tested compounds were found to inhibit the generation of reactive oxygen species (ROS) and lipid peroxidation in the prefrontal cortex and hippocampus of mice [52].

Table 1.7: Optimization study of organocatalytic reaction.

Entry	Organocatalyst (mol %)	Temperature (°C)	Yield (%)
1	DBU (10)	25	15
2	DBU (10)	70	82
3	DBU (20)	70	80
4	DBU (5)	70	53
5	Pyrrolidine (10)	70	–
6	Diethylamine (10)	70	–

Takemoto's group developed the synthesis of the alkaloid (–)-epibatidine (**178**) *via* enantioselective double Michael addition reaction (Figure 1.49). It binds to nicotinic acetylcholine receptors (nAChR) to produce its action. It involves Michael addition of the γ,δ-unsaturated-ketoester to the nitroalkene in presence of KOH, catalyzed by bifunctional thiourea-based organocatalyst to produce nitroalkane which undergoes cyclization to generate polysubstituted cyclohexene with high yield. Further, the total synthesis of (–)-epibatidine was achieved in seven steps [53].

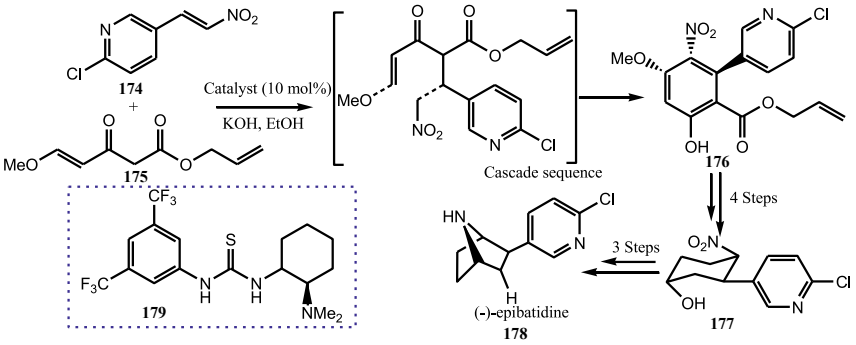


Figure 1.49: Synthesis of (–)-epibatidine.

Liu et al. demonstrated the synthesis of a series of chiral 2-ethylthio-thiazolone derivatives (**182**) (Figure 1.50) via enantioselective aza-Mannich addition. It involves the reaction between thiazolones (**180**) and N-tosylimines (**181**) *via* cinchona alkaloid as a

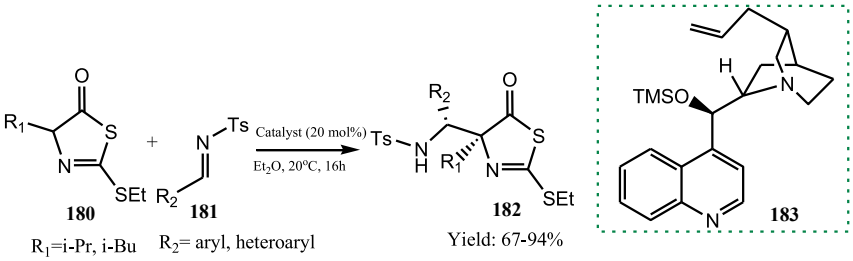


Figure 1.50: Synthesis of thiazolone derivatives.

catalyst. All the compounds were screened for their anticancer activity against human cell cancer lines by using the MTT assay [54].

Brown et al. performed the organocatalytic synthesis of dihydropyrimidinone (**187**) derived guanidine derivatives in presence of (+)-cinchonine and (–)-cinchonidine as catalyst (Figure 1.51). These compounds are found to have anti-malarial activity [55].

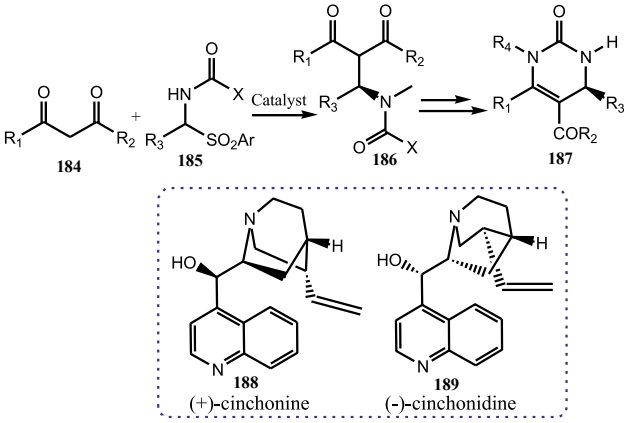


Figure 1.51: Synthesis of dihydropyrimidinones derivatives.

The synthesis of (+)-galipinine (**193**) is performed *via* binolphosphoric acid-catalyzed enantioselective cascade reduction. It involves the stepwise hydride transfer from the Hantzsch ester to quinoline that produces the corresponding tetrahydroquinoline in excellent yields (Figure 1.52). It was found that (+)-galipinine exhibited antimalarial activity against *Plasmodium falciparum* for the chloroquine-resistant strains [56].

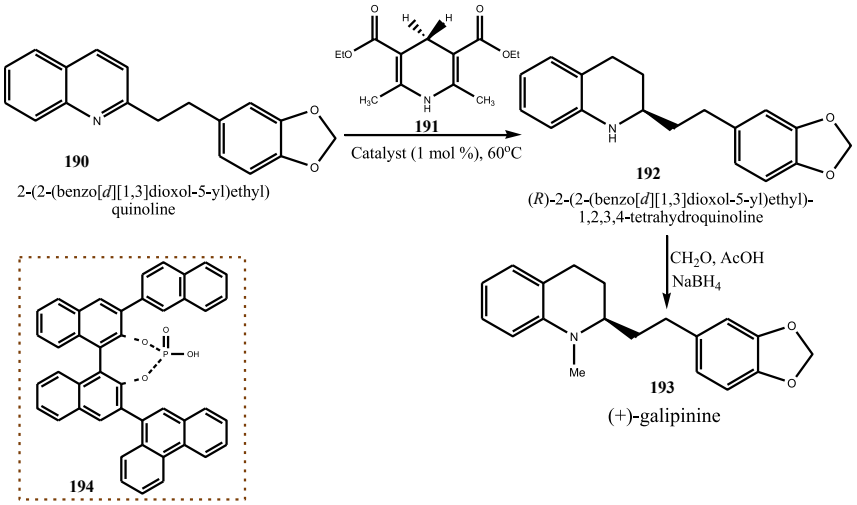


Figure 1.52: Synthesis of (+)-galipinine.

Herrera et al. described the synthesis of anticoagulant (R)-warfarin by using primary aromatic diamines as organocatalysts (Figure 1.53). It involves the Michael asymmetric addition reaction of 4-hydroxycoumarins (**195**) with enones (**196**). Warfarin (**197**) is chemically called 4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one. It is mainly used for the treatment of blood clotting such as pulmonary embolism and deep vein thrombosis [44].

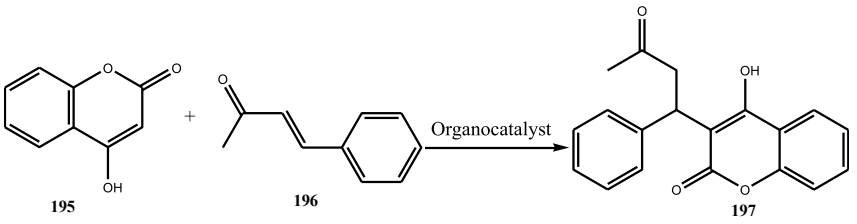


Figure 1.53: Synthesis of (*R*)-warfarin.

Veverkova et al. demonstrated the Michael addition reaction for the synthesis of GABAergic drugs (baclofen **200**) catalyzed by Squaramide (Figure 1.54). It involves the reaction between dimethylmalonate and β-nitrostyrenes. Baclofen is chemically called 4-amino-3-(4-chlorophenyl)butanoic acid. Similarly, another approach involves the addition of nitromethane to cinnamaldehydes to produce baclofen [58].

Tolmetin (**204**) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic activities. It is used for the treatment of

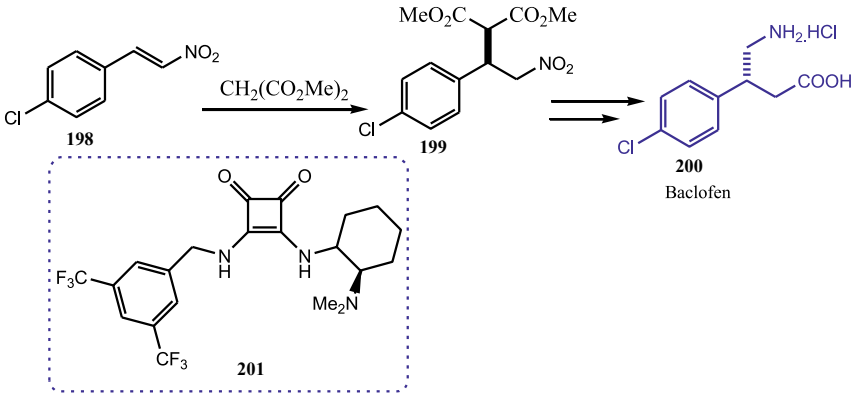


Figure 1.54: Synthesis of Baclofen catalyzed by Squaramide.

osteoarthritis and rheumatoid arthritis. It produces its activity by inhibiting the enzyme prostaglandin synthase. It is chemically known as 1-methyl-5-*p*-toluoylpyrrole-2-acetic acid. The synthesis of Tolmetin is carried out by Friedel–Crafts acylation *via* DBN (1,5-diazabicyclo[4.3.0]non-5-ene) as catalyst (Figure 1.55) [59].

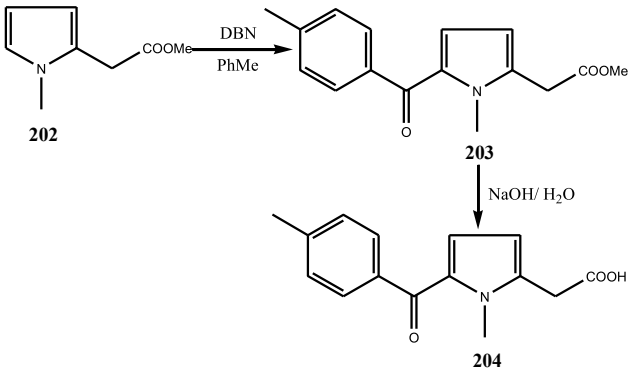


Figure 1.55: Synthesis of Tolmetin *via* DBN.

Merck has developed the chiral phase-transfer organocatalytic (PTC) reaction for the synthesis of (+)-Indacrinone (MK-0197) **206** during 1984. Chemically, Indacrinone is 2-[(6,7-dichloro-2-methyl-1-oxo-2-phenyl-3H-inden-5-yl)oxy]acetic acid. It is used as a uricosuric agent for the management of gout by reducing the reabsorption of uric acid (Figure 1.56) [60].

Pfizer has developed antiretroviral drug like Maraviroc (**208**) for the treatment of AIDS. It produces its activity by acting against human immune deficiency virus (HIV). It is a chemokinereceptor-5 (CCR-5) antagonist. It belongs to the class of compounds

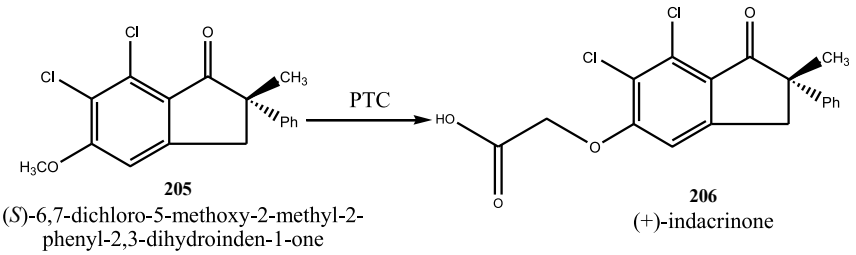


Figure 1.56: Synthesis of (+)-Indacrinone *via* PTC.

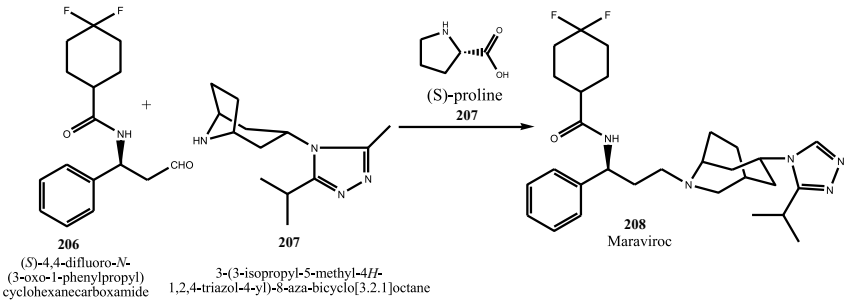


Figure 1.57: Organocatalytic synthesis ofMaraviroc via (*S*)-proline.

called tropane alkaloid. The synthesis of Maraviroc is performed via (*S*)-proline-derived catalyst (**207**) (Figure 1.57) [61].

The enantio-selective organocatalytic synthesis of (–)-Paroxetine (**212**) is carried out with excellent yield through combined thiourea-cinchona (**211**) [62]. Paroxetine is selective serotonin reuptake inhibitor (SSRI). It is a blockbuster anti-depressive drug. It is used for the management of anxiety, depression and obsessive compulsive disorders (Figure 1.58).

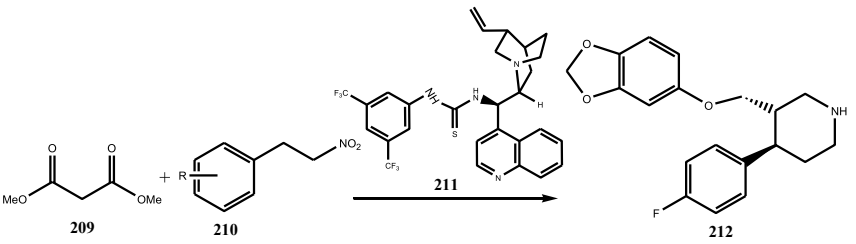


Figure 1.58: Synthesis of Paroxetine via combined thiourea-cinchona.

The organocatalytic synthesis of (–)Oseltamivir (**216**) is catalyzed by Enamine [63]. It is found to be effective against infections caused by influenza viruses (Figure 1.59). The catalysis process involves the use of three reagents such as diphenylprolinol silyl ether,

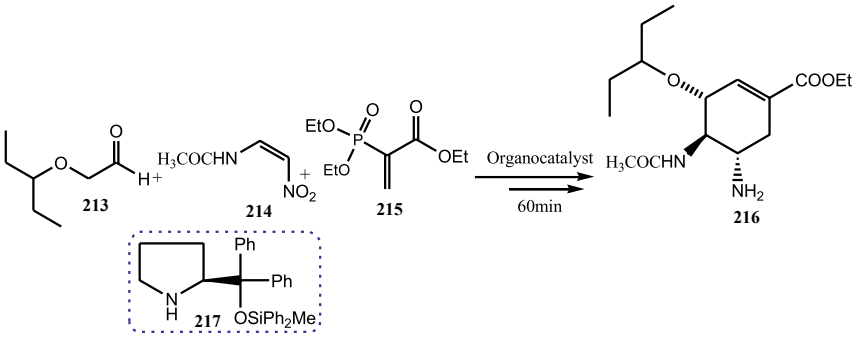


Figure 1.59: Synthesis of Oseltamivir catalyzed by Enamine.

thiourea, and acid for rapid asymmetric Michael reaction with formation of excellent diastereo- and enantioselective product.

(–)-Anisomycin (**219**) is synthesized *via* D-proline-catalyzed tandem *α*-amination-olefination reaction. Anisomycin is an antibiotic used clinically for the management of amoebic dysentery (Figure 1.60). It displays its activity against pathogenic protozoa and fungi. Anisomycin is also applied for the treatment of vaginitis [64].

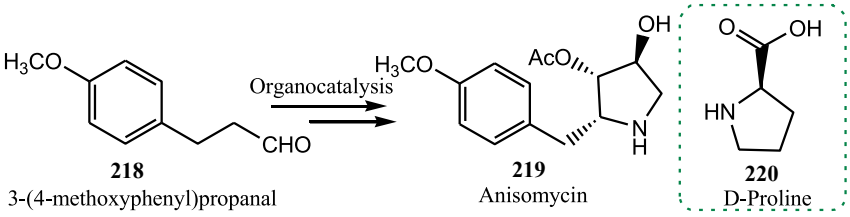


Figure 1.60: Organocatalytic synthesis of (–)-Anisomycin.

Laninamivir (**222**) is a long-acting neuraminidase inhibitor and is used for the treatment of infection caused by both influenza A and B viruses. It is under phase III clinical trial and is administered by nasal route. The synthesis of Laninamivir (**222**) is based on a Michael addition reaction (Figure 1.61). Organocatalytic intramolecular

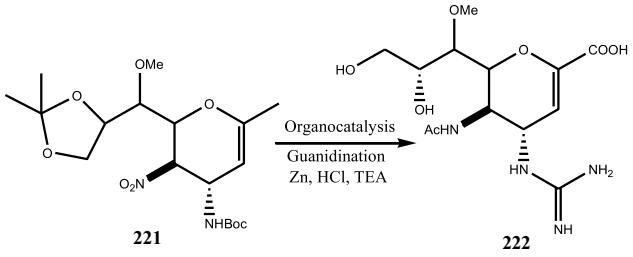


Figure 1.61: Synthesis of Laninamivir.

Michael addition reactions are the potential synthetic approach for the preparation of cyclic compounds with stereogenic centers [65].

Benzoxaborole (**225**) is boron-containing molecule with antibacterial, anti-viral, and anti-parasitic activities. It also acts as a β-lactamase inhibitor. The Lewis acidity property of the boron and its easy conversion from trigonal to tetrahedral geometry facilitates benzoxaboroles to bind with the active site of various enzymes and thereby inhibiting their activities. The enantioselective synthesis of 3-substituted benzoxaboroles is carried out by asymmetric oxa-Michael addition of hydroxyl group attached to the boronic acid which is activated by the cinchona alkaloid based chiral aminosquaramide catalysts (**226**) (Figure 1.62). This method is applied significantly to develop drug molecule like tavaborole (antifungal) and other drugs currently under clinical trials for psoriasis include AN2728 and AN2898 (Figure 1.63) [34]. Similarly, SCYX-7158/AN5568 (**238**) has also studied clinically for the management of human trypanosomiasis [66].

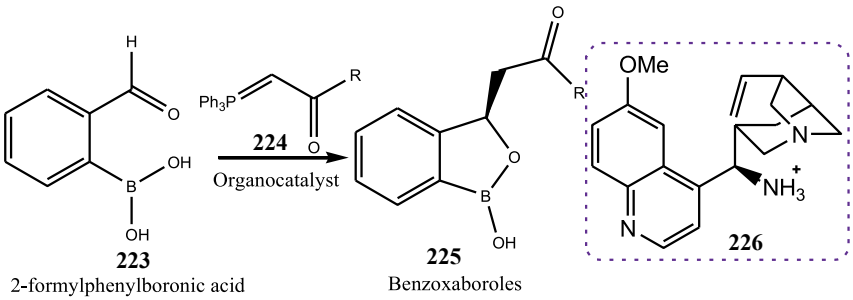


Figure 1.62: Synthesis of Benzoxaborole.

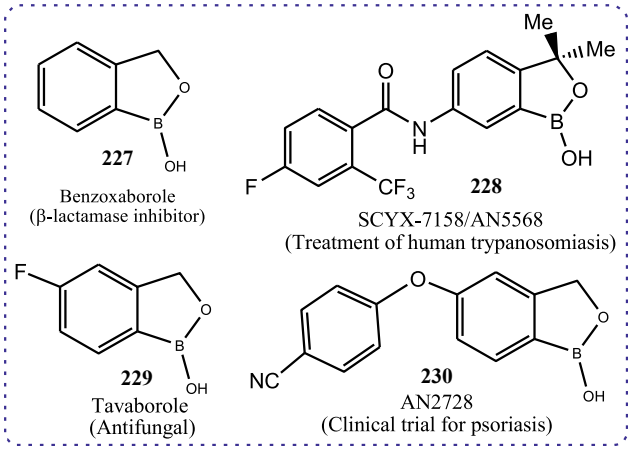


Figure 1.63: Clinically available drugs with benzoxaborole moiety.

The synthesis of Baccatin III (**233**) involves the reaction of 2-methyl-2-(3-oxobutyl) cyclohexane-1,3-dione (**231**) *via* 8a-methyl-3,4,8,8a-tetrahydro-naphthalene-1,6(2*H*,7*H*)-dione (**232**) in the presence of catalyst (S)-Proline (**207**) (Figure 1.64). Baccatin III is used as a precursor to synthesize the anti-cancer drug like paclitaxel (Taxol) [67].

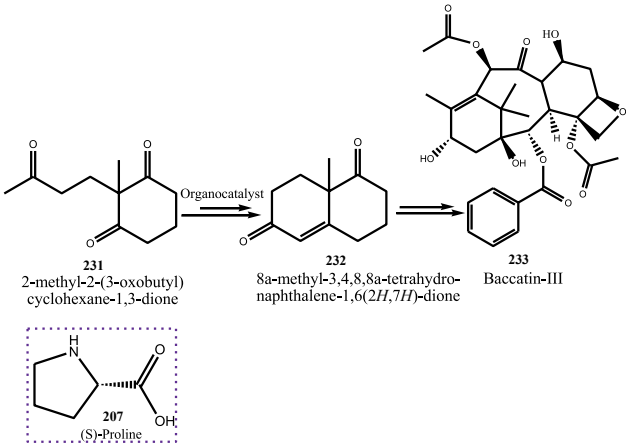


Figure 1.64: Synthesis of Baccatin III.

(*R*)-rolipram (**236**) is synthesized by using the combined thiourea-cinchona catalyst through enantio-selective Michael addition of nitro-olefin (**234**) (Figure 1.65). It is found to have phosphodiesterase inhibitor with antidepressant activity [68].

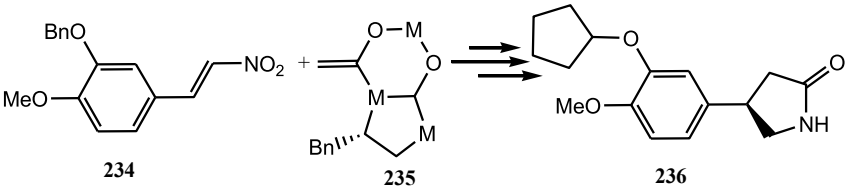


Figure 1.65: Synthesis of (R)-rolipram.

Organocatalytic method is most commonly applied in several chemical syntheses through Bakers' yeast. This yeast is generated by the fermentation of yeast strain *Saccharomyces cerevisiae* under aerobic condition. Baker's yeast contains enzymes that can reduce the carbonyl group into a hydroxyl group with a high product yield and thereby making it a useful technique for bio-transformations of drug substances. Fenfluramine (**239**) is chemically known as 3-trifluoromethyl-N-ethylamphetamine. It possess anorectic property and is used clinically for the treatment of obesity.

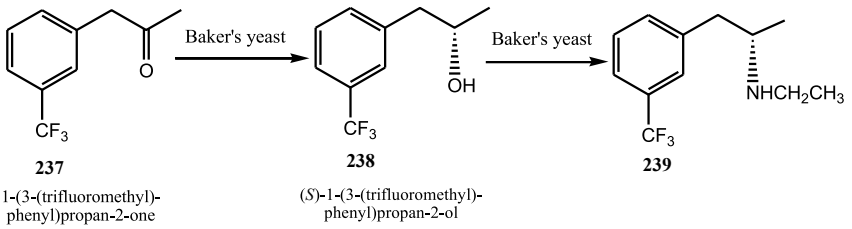


Figure 1.66: Synthesis of Fenfluramine.

Fenfluramine is synthesized by the reaction of 1-(3-(trifluoromethyl)phenyl)propan-2-one (**237**) in the presence of Baker's yeast (Figure 1.66) [69].

The engineered yeast systems can afford artemisinin (**242**) or its precursor artemisinic acid that can be converted to artemisinin via chemical reactions (Figure 1.67). Chemically, Artemisinin is sesquiterpene *endo*-peroxide lactone. The presence of an *endo*-peroxide bridge in Artemisinin is required for therapeutic activity. So, it is used for the treatment of malaria [70].

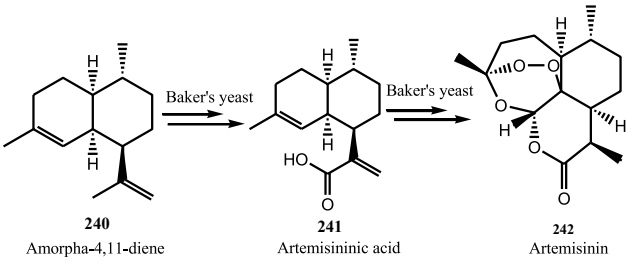


Figure 1.67: Synthesis of artemisinin.

The synthesis of ephedrine can be performed in two steps by using Baker's yeast (Figure 1.68). First of all, phenyl acetyl carbinol is synthesized from benzaldehyde (**243**) and pyruvate (**244**) in the presence of Baker's yeast. Then, the phenylacetyl carbinol (**245**) reacts with methylamine (**246**) in the presence of Baker's yeast to produce ephedrine (**247**). Ephedrine possesses α- and β-adrenergic activity and is used for the treatment of asthma and nasal congestion [71].

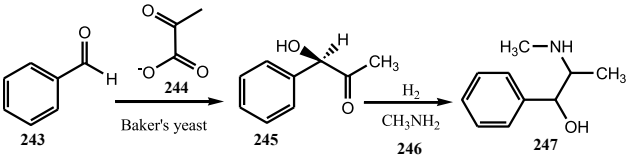


Figure 1.68: Baker's yeast mediated synthesis of ephedrine.

Denopamine is a β_1-adrenergic receptor agonist with cardiotonic property. It is used for the management and treatment of angina and congestive heart failure (CHF) [72]. Chemically, Denopamine is chemically known as 4-(2-(3,4-dimethoxyphenethylamino)-1-hydroxyethyl)phenol (Figure 1.69). It is synthesized by different steps such as a) ethyl 2-hydroxy-2-(4-hydroxyphenyl)acetate (**249**) is obtained from ethyl 2-(4-hydroxyphenyl)-2-oxoacetate (**248**) in the presence of Baker's yeast b) preparation of compound **251** from ethyl-2-hydroxy-2-(4-hydroxyphenyl)acetate (**249**) in the presence α-hydroxy pyridine and xylene c) finally Denopamine (**252**) is obtained from *N*-(3,4-dimethoxyphenethyl)-2-hydroxy-2-(4-hydroxyphenyl)acetamide (**251**) in the presence of B_2H_6 and THF.

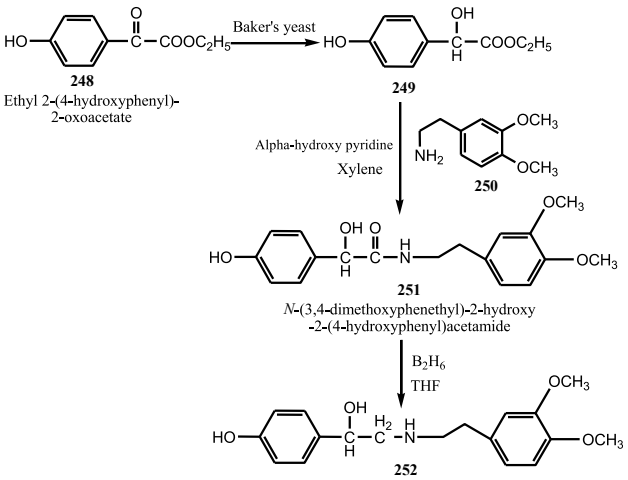


Figure 1.69: Baker's yeast mediated synthesis of Denopamine.

Wang et al. performed the organocatalytic enantioselective Michael–Michael cascade reaction for the production of 3,3′-spirooxindoles fused with tetrahydrothiopyrans **255** (Figure 1.70) with good yield (55–74%). This compound is a highly

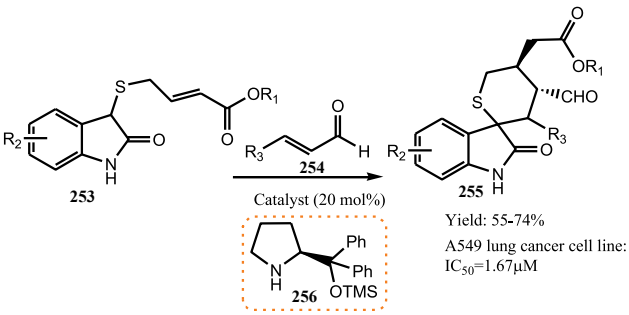


Figure 1.70: Synthesis of 3,3′-spirooxindoles fused with tetrahydrothiopyrans.

functionalized scaffold and is considered a new class of p53-MDM2 protein-protein interaction inhibitors (K_D = 2.2 μM) with promising antitumor activity (A549 lung cancer cell line IC_{50} = 1.67 μM) [73].

Fujita et al. demonstrated the synthesis of different aziridine-oxazolone compounds (**259**). It involves the heating of α-azideacrylates at 150 °C in organic solvent tetrahydrofuran (THF) to obtain 2*H*-azirines and then reacts with oxazolones in presence of organocatalysts to produce corresponding aziridine-oxazolone derivatives (Figure 1.71). The reaction proceeds at the C_2 position of the oxazolones to generate products with high yield and tetra-substituted stereogenic centers with high diastereo and enantio-selectivity. For this synthesis, the organocatalyst is derived from cinchona alkaloid. The newly synthesized compounds exhibit anti-tumor activity [74].

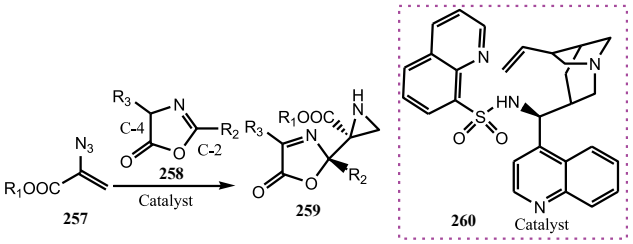


Figure 1.71: Synthesis of aziridine-oxazolone compounds.

It is demonstrated that ascorbic acid (Vitamin C) **266** is an efficient and versatile organocatalyst used for preparing different organic molecules with diverse pharmacological properties. Huang et al. described the efficient methods for the synthesis of dispiro [tetrahydroquinoline-bis(1,3-dioxane-4,6-dione)] derivatives **265** in the presence of L-ascorbic acid as an efficient organocatalyst (Figure 1.72). It involves the four-component reaction between 1,3-dioxane-4,6-dione (**261**), aromatic aldehydes (**262**), arylamines (**263**), and acetone (**264**). This method generates the final product *via* different reaction mechanisms including Michael, Diels–Alder, Knoevenagel, and intra-molecular reaction. The tetrahydroquinoline derivatives demonstrate a wide range of biological activities such as anti-proliferative, antifungal, anticancer, and anti-tubercular, etc. [75].

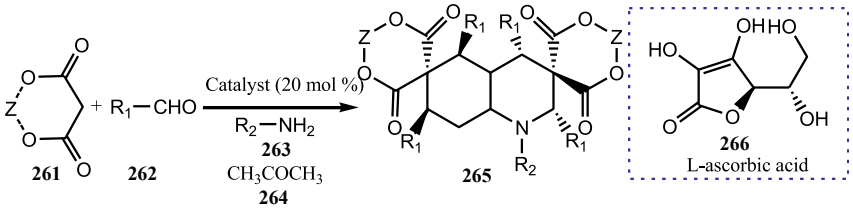


Figure 1.72: Synthesis of dispiro[tetrahydroquinoline-bis(1,3-dioxane-4,6-dione)] derivatives.

Vitor et al. performed the synthesis of cytosporone analogs AMS35BB (**269**) and AMS35AA (**270**) in the presence of ascorbic acid as catalyst (Figure 1.73). Cytosporones is the class of octaketide resorcinolic lipids that exhibits diverse biological properties such as bactericidal, fungicidal, and cytotoxic activities etc. The starting material used for the preparation of AMS35AA and AMS35BB is 3,5-dimethoxy benzoic acid [76].

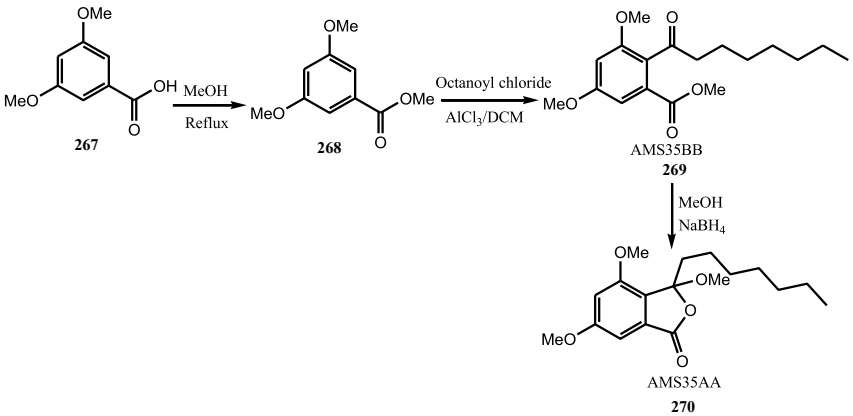


Figure 1.73: Synthesis of cytosporone analogs (AMS35AA and AMS35BB).

1.4 Conclusions

The small organic molecules as catalysts are used significantly in drug synthesis. Organocatalysts are more advantageous in comparison to metallic-catalysts including readily available, efficient, selectivity, economic, non-toxic, recyclable, and stability in air and water. Enantioselective organocatalytic synthesis acts as a potential approach to speed up the development of new chiral molecules with diverse chemical structures and therapeutic potentials. Currently, chiral organocatalysts like proline, pyrimidones, guanidine, and imidazolidone play a major role in synthesis due to high enantioselective catalytic activities. Further experiments are required to reveal the mechanism of the transformation in organic synthesis. This review highlights the involvement of different organocatalysts in drug synthesis.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
Br	Bromine
CCR	Chemokine receptor

Cl	Chloro
DMSO	Dimethyl sulfoxide
HCN	Hydrogen cyanide
HIV	Human immunodeficiency virus
IMAMR	Intra-molecular aza-Michael reaction
KOH	Potassium hydroxide
NaOH	Sodium hydroxide
NOBIN	2-amino-2′-hydroxy-1,1′-binaphthy
NSAID	Non steroidal anti-inflammatory drug
P-BEMP	*N*-phenyl-tris(di-methylamino)iminophosphorane
PTC	Phase transfer catalysis
TADDOLS	Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TEA	Triethylamine

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Hélène Pellissier*

2 Organocatalytic total synthesis of bioactive compounds based on one-pot methodologies

Abstract: The combination of one-pot methodologies to asymmetric organocatalysis allow a green and direct access to many types of complex highly functionalized chiral products, including important key intermediates in total syntheses of important bioactive compounds. A series of chiral organocatalysts have already been successfully applied to such syntheses. This report collects major developments in the total synthesis of biologically active products based on the use of enantioselective organocatalytic domino/tandem reactions as key steps. It is divided into two parts dealing successively with reactions based on the use of proline-derived catalysts and other organocatalysts.

Keywords: asymmetric catalysis, bioactive products, one-pot reactions, organocatalysis, total synthesis

2.1 Introduction

By avoiding costly purification of intermediates and protection/deprotection steps, one-pot synthetic procedures, such as domino and tandem processes [1–17], constitute a challenge in total synthesis. These powerful reactions allow a direct and economic route to sophisticated and highly functionalized molecules starting from simple materials. Thanks to the advent of asymmetric catalysis, a number of asymmetric catalytic versions of these economic methodologies have been employed as key steps in the synthesis of many bioactive products [18–34]. In contrast with metal catalysts [35–45] which are often toxic, cost, moisture sensitivity, green organocatalysts present the advantages to be cheaper, robust, non-toxic, more stable, readily available, and inert towards moisture and oxygen [46–56]. Moreover, organocatalytic processes are particularly adapted for the total synthesis of drugs related to the absence of metal contamination. Consequently, various types of chiral organocatalysts have been applied to the total synthesis of many biologically important products, spanning from common proline-derived secondary amines to cinchona alkaloids, phosphoric acids, and imidazolidinones among others. This report collects the major developments in the total synthesis of important bioactive products based on the use of asymmetric organocatalytic domino and tandem processes. It is decomposed into two sections, focussing successively with total syntheses employing proline-derived catalysts and other organocatalysts.

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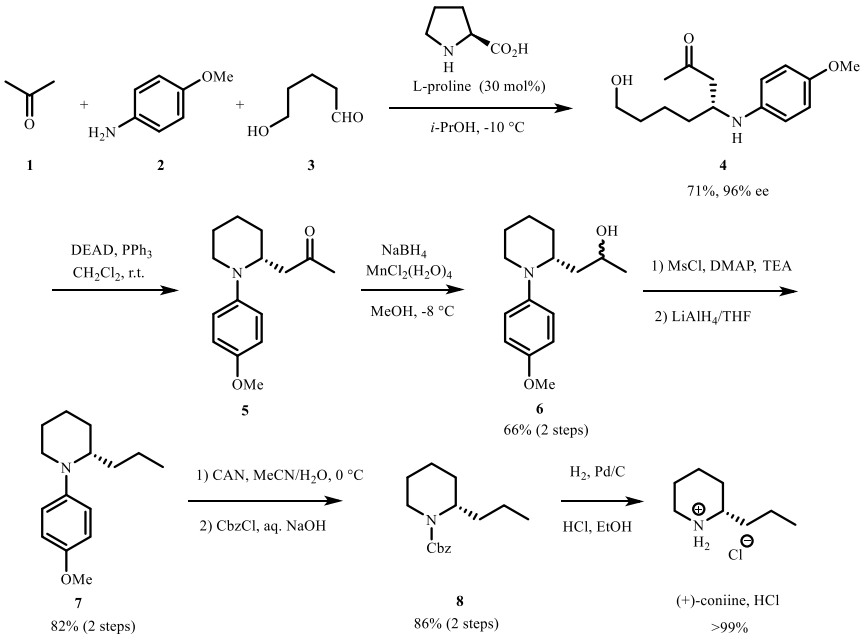
2.2 Proline-derived catalysts

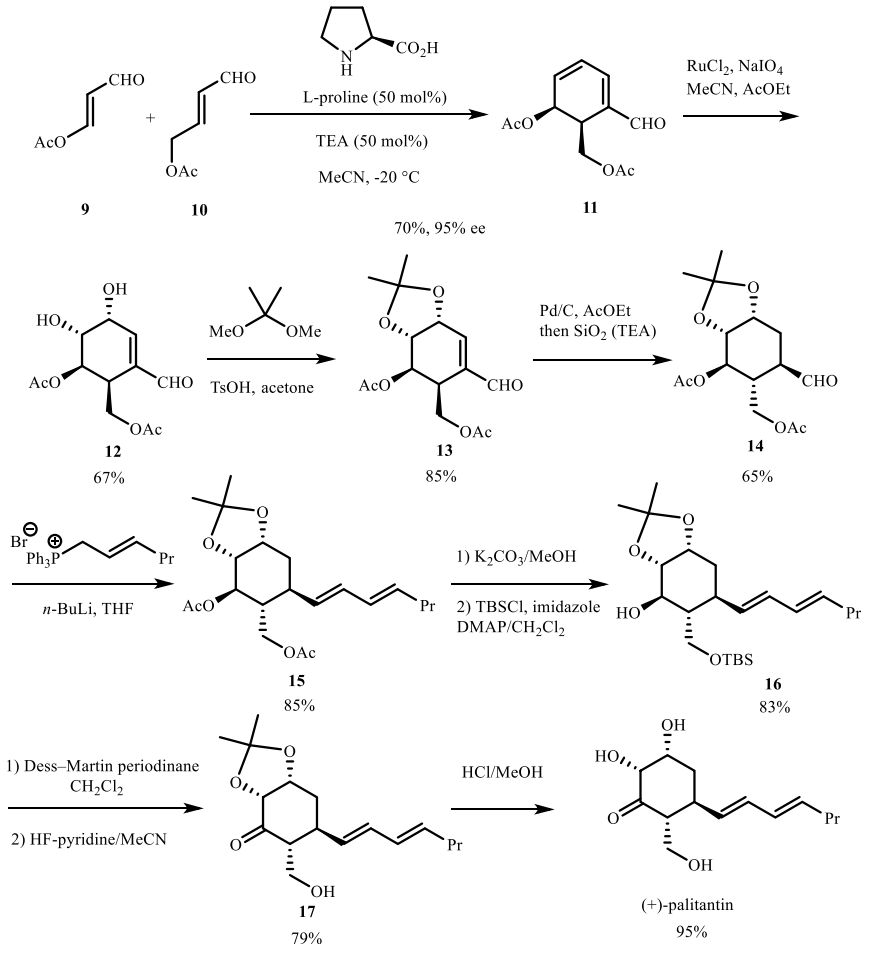
Proline-derived organocatalyts are among the most employed organocatalysts [57, 58]. An early example of using this type of organocatalysts in total synthesis of bioactive products was reported in 2006 by Itoh et al. (Scheme 2.1) [59]. It dealt with the synthesis of alkaloid (+)-coniine, which is a neuro-muscular blocking agent inducing respiratory paralysis. The strategy of the synthesis was based on an asymmetric three-component Mannich reaction organocatalyzed by L-proline. Indeed, the reaction between acetone **1**, *p*-anisidine **2** and 5-hydroxypentanal **3** led to the corresponding chiral Mannich product **4** in both high enantioselectivity (91% ee) and yield (76%). The conversion of this key product into desired (+)-coniine was achieved through seven steps, beginning with its cyclization into piperidine **5** through Mitsunobu reaction followed by reduction of the latter with $NaBH_4$ to give **6** in 66% yield (2 steps). Subsequently, intermediate **6** was mesylated and then reduced with $LiAlH_4$ to give **7** in 82% yield (2 steps). Then, CAN oxidation of **7** followed by Cbz protection led to product **8** in 86% yield (2 steps). A final catalytic hydrogenation of **8** afforded (+)-coniine hydrochloride in quantitative yield.

Later in 2007, a total synthesis of natural product (+)-palitantin, exhibiting anti-HIV, antibiotic, and antifungal activities, was disclosed by Hong et al. [60]. The key step of the synthesis consisted in an enantioselective L-proline-catalyzed Robinson



Scheme 2.1: Synthesis of (+)-coniine.

annulation between α,β-unsaturated aldehydes **9** and **10**, which afforded almost enantiopure (95% ee) cyclohexadiene carbaldehyde **11** in good yield (70%) (Scheme 2.1). This key intermediate was converted into expected (+)-palitantin through nine supplementary steps, beginning with its dihydroxylation into diol **12** achieved with 67% yield. Diol **12** was then protected into acetonide **13** with 85% yield, and then hydrogenation yielded aldehyde **14** in 65% yield. Wittig reaction of the latter with (2*E*)-hexenyl triphenylphosphonium bromide led to diene **15** in 85% yield. Further hydrolysis of **15** followed by protection provided alcohol **16** in 83% yield. Subsequent oxidation of **16** by Dess–Martin periodinane, followed by deprotection of the TBS ether provided acetonide **17** with 79% yield. Finally, deprotection of acetonide **17** afforded (+)-palitantin in 95% yield.

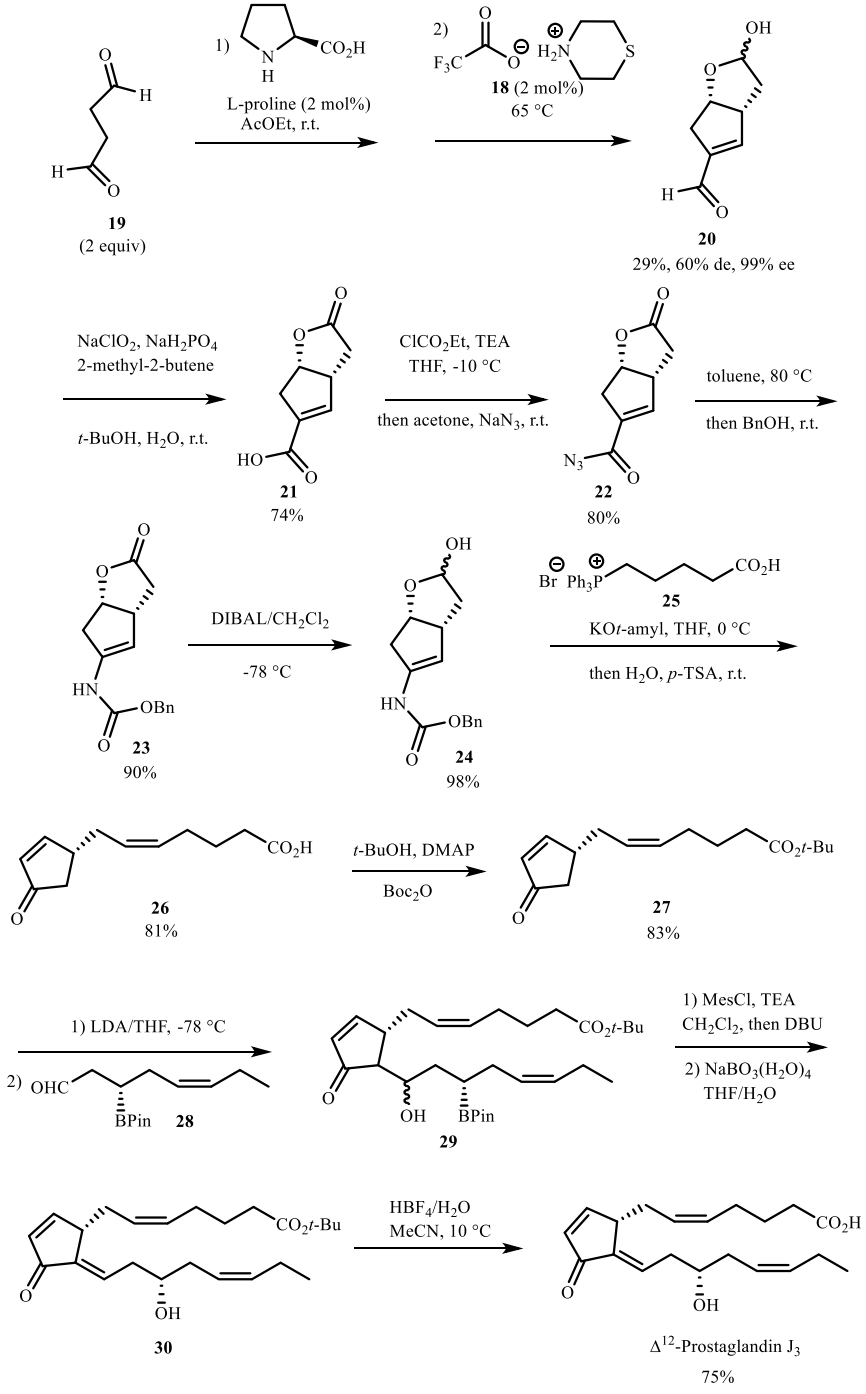


Scheme 2.2: Synthesis of (+)-palitantin.

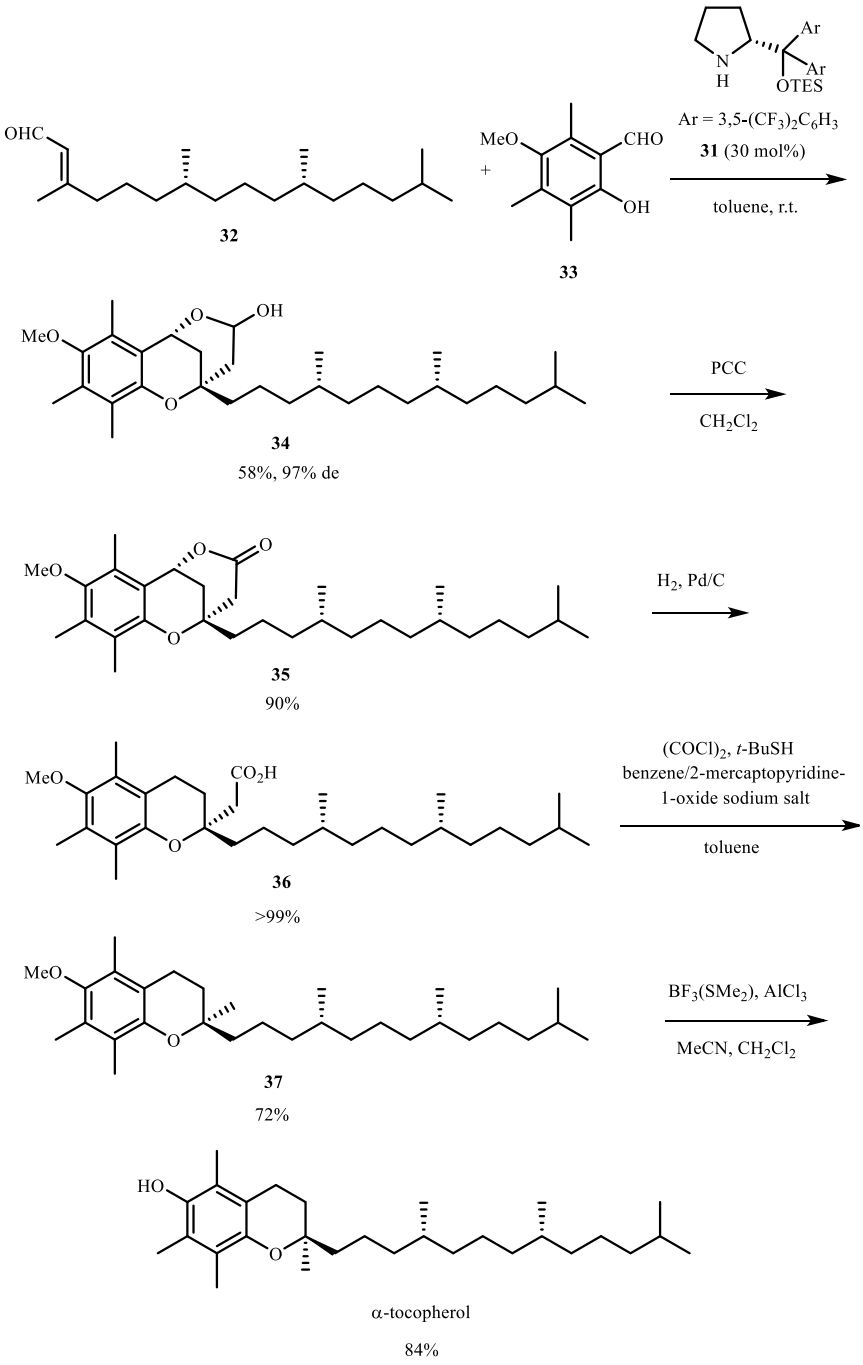
In 2018, an enantioselective tandem double aldol reaction catalyzed by simple L-proline and achiral thiomorpholinium trifluoroacetate **18** was developed by Aggarwal et al. as key step in a total synthesis of Δ^{12}-prostaglandin J_3 exhibiting anti-leukemic properties [61]. This one-pot two-step aldol dimerization of succinaldehyde **19** led to the corresponding chiral bicyclic enal intermediate **20** in 29% yield, 60% de and 99% ee (Scheme 2.3). This product was converted through 10 supplementary steps into Δ^{12}-prostaglandin J_3. The sequence began with the oxidation of the aldehyde group in **20** into carboxylic acid **21** with 74% yield. Then, the latter was converted into acyl azide **22** in 80% yield. Heating **22** in toluene effected a Curtius rearrangement leading to an isocyanate, which was trapped with benzyl alcohol to give carbamate **23** in 90% yield. The latter was then reduced to hemiacetal **24** in the presence of DIBAL with 98% yield. Then, Wittig reaction of **24** with phosphonium salt **25** provided the corresponding enamide which was not isolated but directly hydrolyzed and then dehydrated to afford enone **26** in 81% yield. The latter was further converted into *t*-butyl ester **27** in 83% yield. This product subsequently underwent aldol condensation with β-boryl aldehyde **28** to give alcohol **29** as a mixture of epimers. The latter was treated with MesCl and TEA to afford the corresponding mesylate, which underwent elimination in the presence of DBU to produce exclusively the corresponding *E*-configured elimination product. The resulting boronic ester was oxidized into secondary alcohol **30** using $NaBO_3(H_2O)_4$ in 23% overall yield (3 steps). Finally, treatment of **30** with HBF_4 yielded expected Δ^{12}-prostaglandin J_3 in good yield (75%).

However, proline-derived catalysts have assumed higher and higher importance and are often named "Jorgensen-Hayashi" catalysts. In 2008, a synthesis of the most important member of the vitamin E family, namely α-tocopherol, was developed by Woggon et al. on the basis of an enantioselective domino aldol/oxa-Michael reaction (Scheme 2.4) [62]. Proline-derived amine catalyst **31** was employed to promote this reaction between α,β-unsaturated aldehyde **32** and aldehyde **33**, which led with moderate yield (58%) to chiral tricyclic hemiaminal **34** as almost single diastereomer (97% de). This key product could be transformed into desired α-tocopherol in only four steps. The first one consisted in its oxidation with PCC into lactone **35** achieved with 90% yield. Then, this benzylic lactone was quantitatively hydrogenated into carboxylic acid **36**, which was further submitted to a Barton decarboxylation procedure to give α-tocopherol ether **37** in 72% yield and 94% de. Final cleavage of the methyl ether of **37** by treatment with $BF_3(SMe_2)/AlCl_3$ yielded expected α-tocopherol with 84% yield.

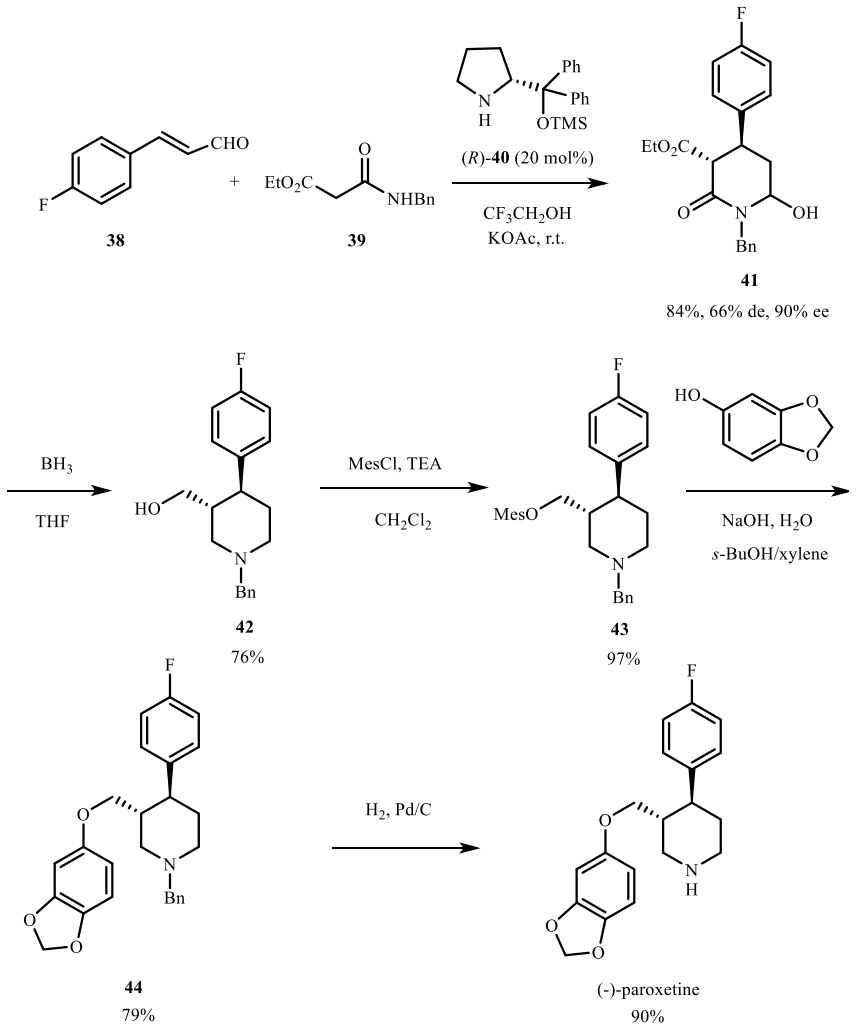
In 2009, Rios et al. described a highly enantioselective synthesis of piperidines through domino Michael/cyclization reaction of α,β-unsaturated aldehydes **38** with amidomalonates **39** catalyzed by chiral proline-derived amine (*R*)-**40** [63]. Among these products, chiral piperidine **41**, obtained with 84% yield, 66% de and 90% ee, was used as key intermediate in a synthesis of (-)-paroxetine which is a selective serotonine reuptake inhibitor drug. As shown in Scheme 2.5, domino product **41** was further converted into primary alcohol **42** with 76% yield by treatment with BH_3. After subsequent protection of the latter into the corresponding mesylate **43** achieved with 97% yield,



Scheme 2.3: Synthesis of Δ^{12}-prostaglandin J_3.



Scheme 2.4: Synthesis of α-tocopherol.

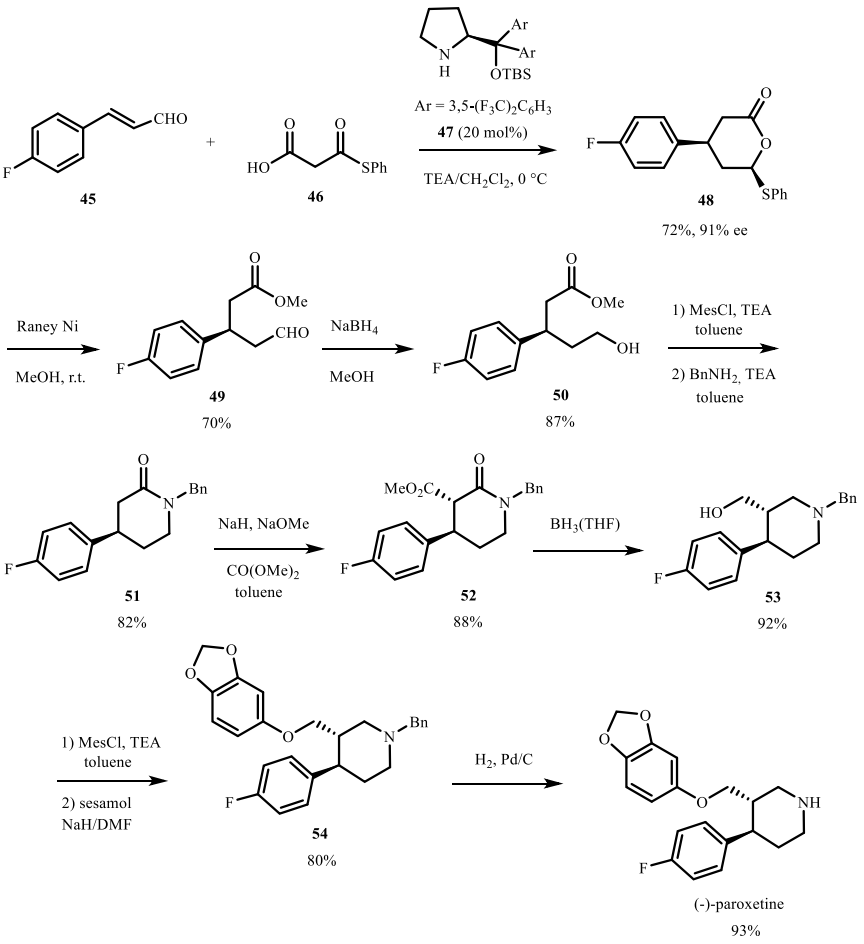


Scheme 2.5: Synthesis of (-)-paroxetine.

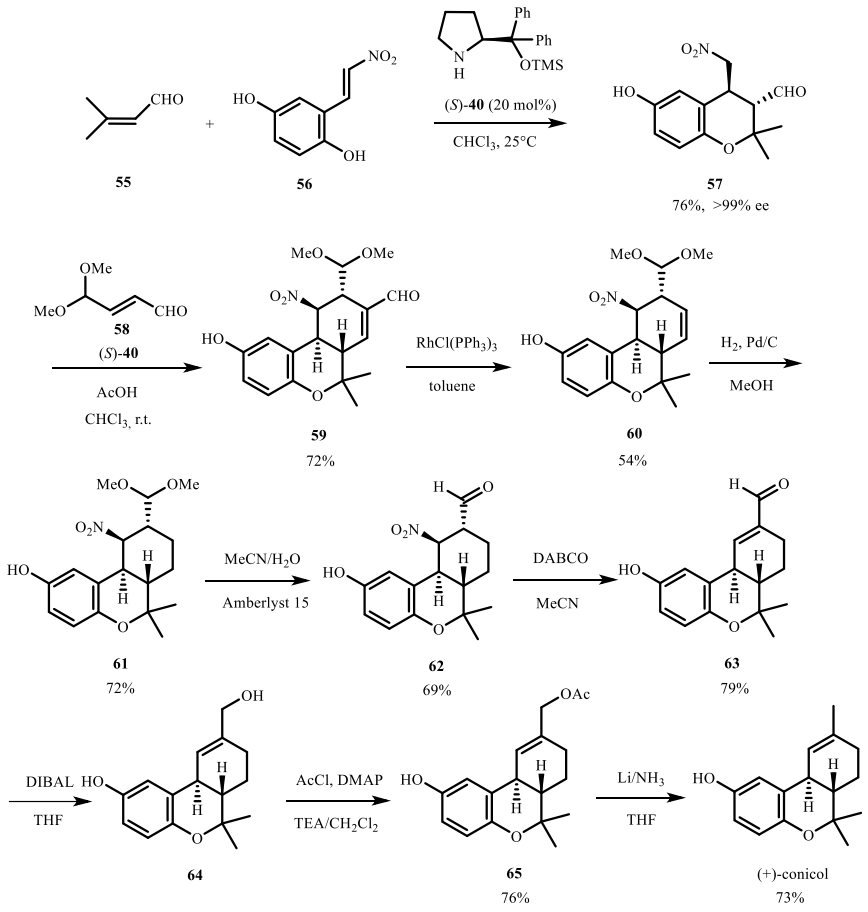
etherification with sesamol led to product **44** with 79% yield. A final deprotection of the *N*-benzyl group in **44** through hydrogenation afforded expected (-)-paroxetine in 90% yield.

Later in 2014, Wang and Sun described another synthesis of (-)-paroxetine the key step of which was another asymmetric domino Michael/cyclization sequence [64]. This occurred with 72% yield and 91% ee between α,β-unsaturated aldehyde **45** and malonic half-thioester **46** in the presence of catalyst **47** (Scheme 2.6). The formed chiral lactone **48** could be further converted in nine supplementary steps into (-)-paroxetine. Firstly, lactone **48** was submitted to nickel-catalyzed ring-opening reaction to give aldehyde

49 in 70% yield. A subsequent reduction of **49** afforded the corresponding chiral primary alcohol **50** in 87% yield. According to previously described works [65], alcohol **50** was mesylated and then submitted to reaction with benzylamine to give the corresponding lactame **51** in 82% yield. A subsequent carboxymethylation gave **52** in 88% yield, which was further reduced into primary alcohol **53** in 92% yield. Then, mesylation followed by reaction with sesamol afforded ether **54** in 80% yield. The latter was finally hydrogenated with 93% yield into expected (-)-paroxetine. This second total synthesis of (-)-paroxetine presents the disadvantage in comparison with that described in Scheme 2.5 to be longer with 10 steps instead of five steps for the former.



Scheme 2.6: Another synthesis of (-)-paroxetine.



Scheme 2.7: Synthesis of (+)-conicol.

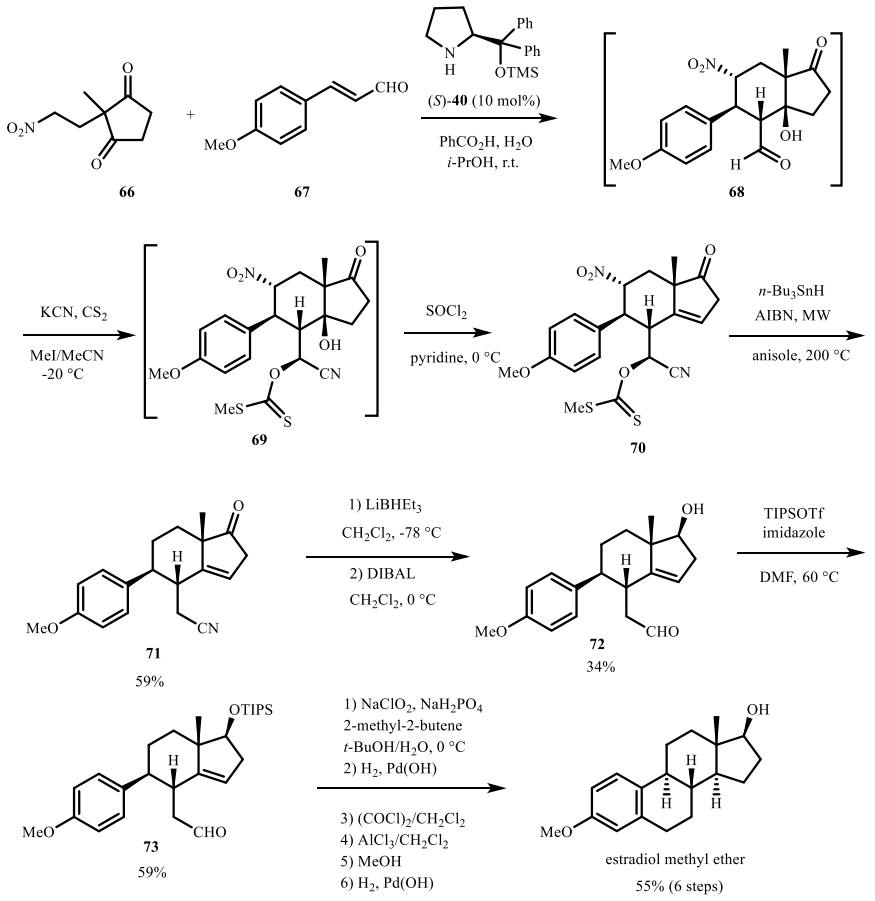
In 2010, Hong et al. developed the first total synthesis of natural and biologically active product (+)-conicol (Scheme 2.7) [66]. The synthesis involved an enantioselective domino oxa-Michael/Michael reaction of 3-methylbut-2-enal **55** with (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol **56** catalyzed by L-proline-derived secondary amine (*S*)-**40**, which afforded the corresponding enantiopure cycloadduct **57** in good yield (76%). This compound was further implicated in a domino Michael/aldol sequence catalyzed by the same organocatalyst through reaction with crotonaldehyde **58**, leading to chiral hexahydro-6*H*-benzo[*c*]chromene **59** in good yield (72%). The latter was submitted to decarbonylation in the presence of Wilkinson catalyst to give alkene **60** in moderate yield (54%). Then, hydrogenation of **60** provided **61** in 72% yield. Hydrolysis of the dimethoxymethyl group in **61** gave product **62** in 69% yield. A subsequent denitration elimination of **62** performed with DABCO led to **63** in 79% yield. Reduction of **63** with

DIBAL afforded primary alcohol **64** in 73% yield. A further acetylation of **64** yielded acetate **65** in 76% yield, which finally underwent lithium reduction to provide expected (+)-conicol with 73% yield.

In order to propose a novel route to estrogenic hormone estradiol, Hayashi et al. developed in 2017 an asymmetric total synthesis of estradiol methyl ether based on the use of a proline-derived organocatalyst [67]. Indeed, the first step of the sequence consisted in an enantioselective domino Michael/aldol reaction of nitroalkane **66** with α,β-unsaturated aldehyde **67** catalyzed by chiral amine (*S*)-**40** to give the corresponding enantiopure bicyclic product **68**. This highly functionalized bicyclo[4.3.0] nonane was not isolated but directly submitted to stereoselective addition of KCN to the carbonyl group of the aldehyde, and then generation of xanthate ester **69**. Again, the latter was not isolated but directly dehydrated upon further addition of $SOCl_2$ in the presence of pyridine to provide enantiopure cyclopentene **70** in 78% yield (3 steps). Subsequently, treatment of **70** with $HSnBu_3$ in the presence of AIBN resulted in the hydrogenolysis of both the nitro and the xanthate ester groups to give intermediate **71** in 59% yield. Then, the ketone moiety in **71** was submitted to diastereoselective reduction in the presence of $LiBHEt_3$ to give the corresponding chiral alcohol. The latter was not isolated but directly treated with DIBAL which resulted in the conversion of the nitrile group into a formyl moiety. The formed hydroxy aldehyde **72** was obtained in 34% yield for the two-step one-pot reaction. The next step was the protection of **72** into the corresponding silyl ether **73** with 59% yield. The latter was then submitted to a one-pot cascade of six reactions detailed in Scheme 2.8, involving successively a Kraus–Pinnick oxidation, an hydrogenation, an acyl chloride formation, a Friedel–Crafts acylation, a TIPS deprotection, and a reduction of benzyl ketone moiety to afford final enantiopure estradiol methyl ether in 55% overall yield (6 steps). It must be noted that this total synthesis consisted finally in only five one-pot reactions along with as low as four purification procedures. Later in 2018, the same authors improved this synthesis, increasing the overall yield from 5 to 6.8% [68].

2.3 Other organocatalysts

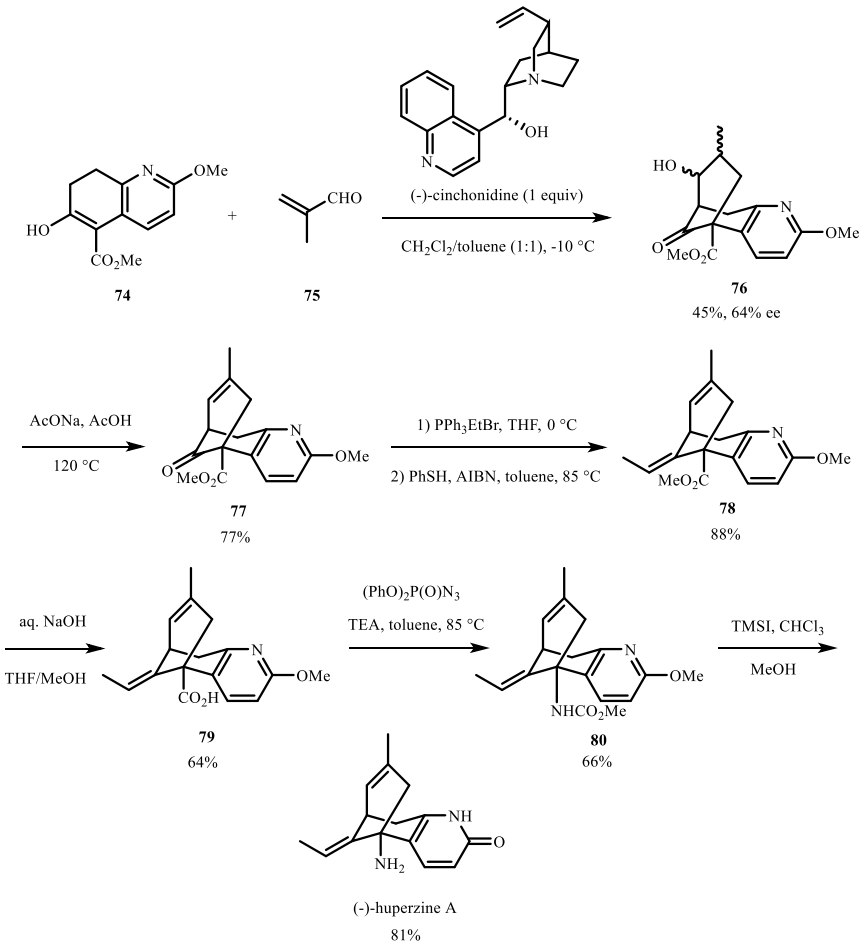
In 1998, Terashima et al. applied for the first time the concept of organocatalysis to the total synthesis of a drug, namely (-)-huperzine A, which is a naturally occurring potent reversible acetylcholinesterase inhibitor agent employed for the treatment of Alzheimer's disease [69]. As shown in Scheme 2.9, the key step of this short synthesis consisted in an enantioselective domino Michael/aldol reaction between β-keto ester **74** and methacrolein **75** organocatalyzed by (-)-cinchonidine, leading to chiral key tricyclic product **76** in both moderate yield (45%) and enantioselectivity (64% ee). The latter was further converted through six supplementary steps detailed in Scheme 2.9 into expected (-)-huperzine A. In a first step, domino product **76** was submitted to dehydration in the presence of acetic acid to give product **77** in 77% yield. The second and third steps



Scheme 2.8: Synthesis of estradiol methyl ether.

consisted in a Wittig reaction of **77** with ethylidenetriphenylphosphorane followed by isomerization of the ethylidene moiety to afford (*E*)-configured ethylenic product **78** in 88% yield (2 steps). A subsequent alkaline hydrolysis of this product led to the corresponding carboxylic acid **79** in 64% yields. Then, a modified Curtius rearrangement of the latter gave amide **80** in 66% yield, which was finally submitted to deprotection in the presence of TMSI to provide expected (-)-huperzine A in 81% yield.

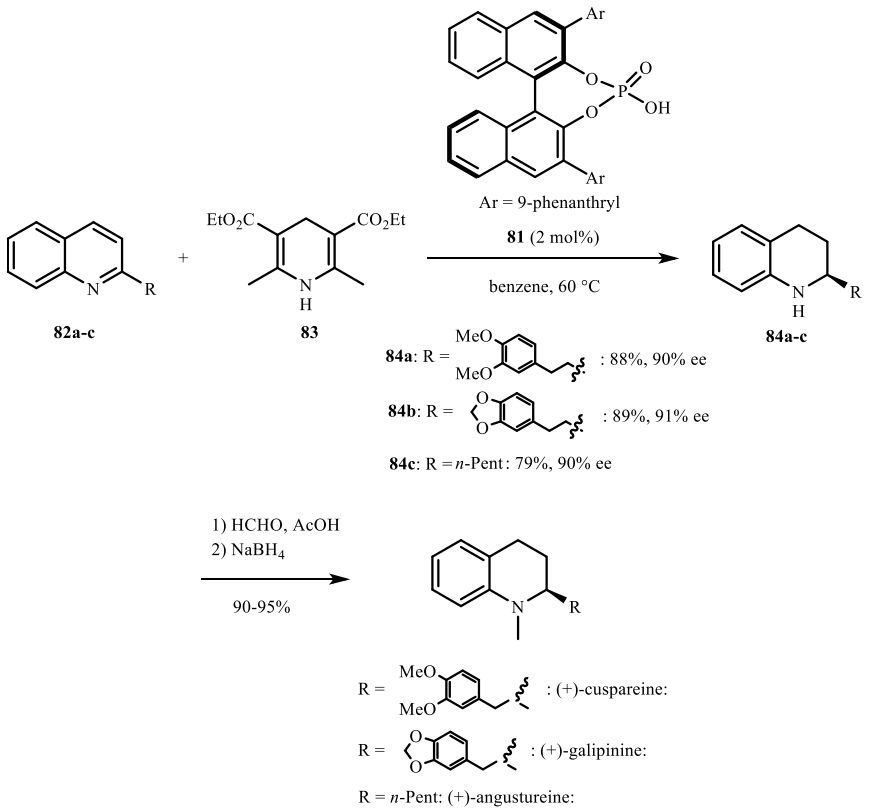
Later in 2006, chiral phosphoric acid **81**, was applied by Rueping et al. to promote the key step of the synthesis of three bioactive tetrahydroquinoline alkaloids, such as (+)-cuspareine, (+)-galipinine and (+)-angustureine [70]. Indeed, Brønsted acid **81** was found to catalyze highly enantioselectively the cascade transfer hydrogenation of 2-substituted quinolines **82a-c** with Hantzsch ester **83**. As shown in Scheme 2.10, this one-pot double-transfer hydrogenation afforded the corresponding chiral tetrahydroquinolines **84a-c** in both high yields (79–89%) and enantioselectivities (90–91%



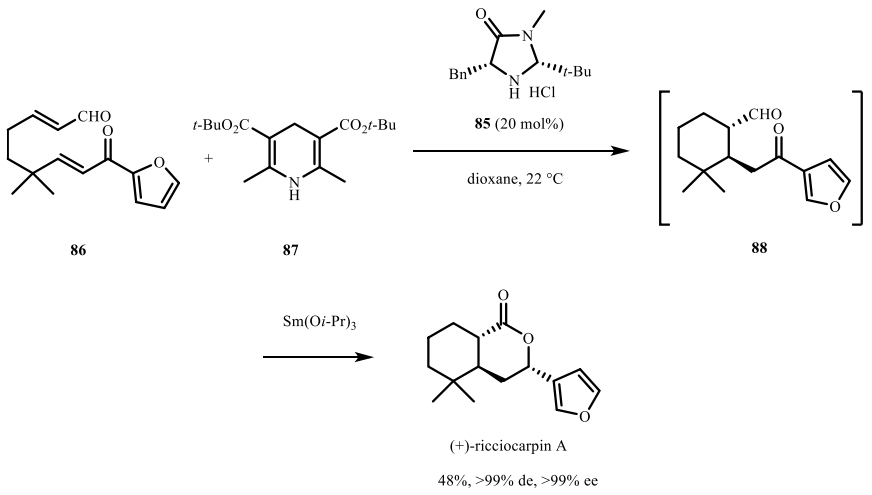
Scheme 2.9: Synthesis of (-)-huperzine A.

ee). The latter were further *N*-methylated to give expected (+)-cuspareine, (+)-galipinine and (+)-angustureine in excellent yields (90–95%).

In 2009, List and Michrowska employed a chiral imidazolidinone catalyst, such as **85**, to promote enantioselective domino conjugate reduction/Michael cyclization reaction between aldehyde **86** and Hantzsch ester **87** [71]. This reaction allowed the synthesis of chiral ketoaldehyde **88** to be achieved. The latter was not isolated, but directly submitted to $Sm(O\textit{i}\text{-}Pr)_3$, undergoing isomerization followed by a highly diastereoselective Tishchenko reaction, which yielded ricciocarpin A, an anti-schistosomiasis agent. Remarkably, this natural product was obtained as a single diastereo- (>99% de) and enantiomer (>99% ee) in 48% yield (Scheme 2.11). This synthesis of ricciocarpin A represented the shortest reported so far.

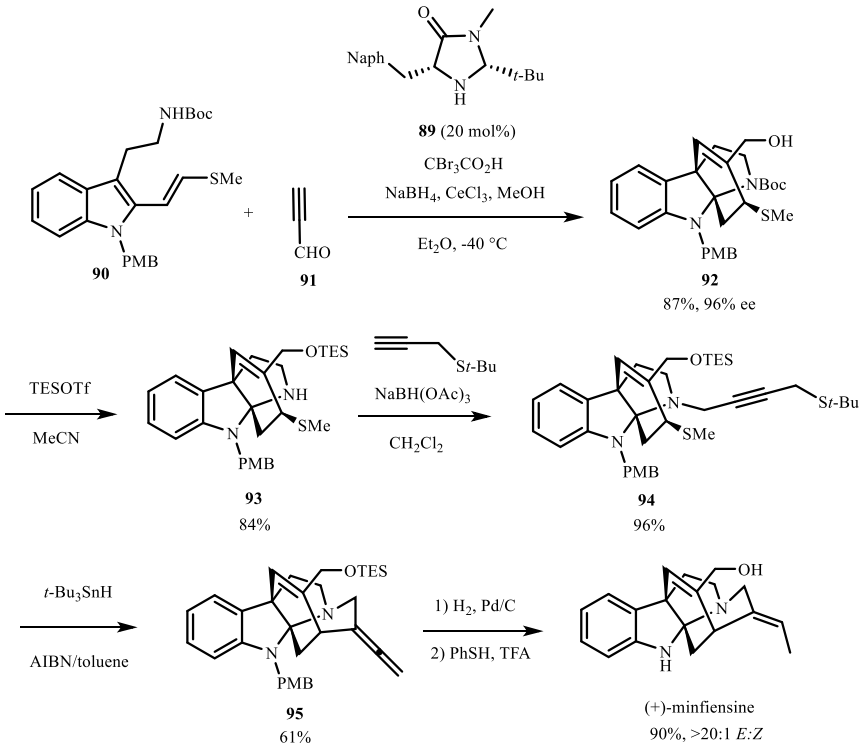


Scheme 2.10: Synthesis of (+)-cuspareine, (+)-galipinine and (+)-angustureine.



Scheme 2.11: Synthesis of ricciocarpin A.

The indole skeleton is widely expanded in medicinal chemistry [72,73]. The same year, MacMillan et al. reported a total synthesis of natural and biologically active (-)-minfiensine the key step of which was an highly enantioselective organocatalytic domino Diels–Alder/amine cyclization reaction building the central tetracyclic pyrroloindoline framework of (-)-minfiensine (Scheme 2.12) [74]. Indeed, the reaction of 2-vinylindole **90** with propynal **91** organocatalyzed by chiral imidazolidinone **89** led to the corresponding chiral tetracyclic pyrroloindoline **92** in both high yield (87%) and enantioselectivity (96% ee). This carbamate was further converted through only five steps into (-)-minfiensine. The first step consisted in the treatment of **92** by TESOTf to provide silyl ether **93** in 84% yields. A reductive amination of this secondary amine **93** with butynal *t*-butyl sulfide was performed in the presence of $NaBH(OAc)_3$ to give intermediate **94** in 96% yield. The latter was further submitted to a radical cyclization, affording allene **95** with 61% yield. Hydrogenation of this allene followed by deprotection in the presence of TFA led to final (-)-minfiensine in both high yield (90%) and *E/Z* diastereoselectivity (>20:1).



Scheme 2.12: Synthesis of (-)-minfiensine.

2.4 Conclusion

This report collects major developments in the use of enantioselective organocatalytic domino/tandem processes for the total synthesis of bioactive products. It demonstrates that a wide variety of one-pot asymmetric reactions catalyzed by chiral green organocatalysts have already allowed a diversity of biologically important products and drugs to be economically synthesized. The most employed organocatalysts employed in these syntheses are proline-derived secondary amines which have allowed the syntheses of products as different as (+)-conicol with >99% ee, (+)-coniine with 91% ee, (+)-paroxetine with 91% ee, estradiol methyl ether with >99% ee, Δ^{12}-prostaglandin J_3 with 99% ee, (+)-palitantin with 95% ee, and α-tocopherol with 97% de. Other types of chiral organocatalysts, such as chiral imidazolidinones, have been used in the key steps of total syntheses of (+)-minfiensine with 96% ee, and (+)-ricciocarpin A with >99% ee. Chiral phosphoric acids also gave success in the total syntheses of (+)-cuspareine, (+)-galipinine, and (+)-angustureine with 91% ee, while cinchona alkaloids were employed to promote the key steps in the synthesis of (-)-huperzine A with 64% ee. In accordance with the huge advent of asymmetric catalysis, more and more organocatalytic asymmetric domino and tandem methodologies were undoubtedly applied as key economic steps in the total synthesis of other bioactive products in the near future.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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Aparna Das and Bimal Krishna Banik*

3 Microwave-induced biocatalytic reactions toward medicinally important compounds

Abstract: Microwaves in the presence of enzymes are used to execute a number of reactions for the preparation of biologically active compounds. The success of microwave-induced enzymatic reactions depends on frequencies, field strength, waveform, duration, and modulation of the exposure. Enzymes under microwave irradiation become activated and this activation is sufficient to investigate simple to complex reactions that were not reported under these reaction conditions before. Enzymatic catalysis together with microwave technology and solvent-free chemical reaction is a nature-friendly procedure. The most interesting reactions that are performed by enzymes in the microwave are documented here with reference to examples that are related to medicinally active molecules.

Keywords: biological activity; enzyme; microwave; organic reactions.

3.1 Introduction

Organic reactions induced by microwave have been widely used for the synthesis of diverse compounds of medicinal significance [1]. A considerable rate enhancement of reactions has been observed. Consequently, a group of researchers has hypothesized that the rate of accelerations is because of the rapid rise of temperature in the reaction media exerted by automated or commercial microwaves. However, some believe that the rate of acceleration of reactions is due to radiation exerted by the microwave. This debate has become very intense, although the main focus to synthesize important molecules and drug candidates have not diminished. Rather, the interest in microwave-induced processes towards the synthesis of medicinally crucial substrates has increased worldwide. Therefore, using this method, a significant number of chiral and achiral potent molecules against diverse medical disorders are prepared. For the preparation of achiral compounds, optically active substrates or catalysts are required. In many instances, asymmetric induction may not be adequate and the chiral compounds may not be optically pure. This results in a weaker medicinal activity of some of the products. On the

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basis of high demand, asymmetric synthesis with enzymes has been introduced in medicinal and organic chemistry. Microwave-induced reactions for the preparation of chiral or achiral molecules using enzymatic pathways are not explored systematically in the past. Recently, however, this area has begun to create interest among scientists. Enzymes have characteristic properties. These are highly active and specific biological catalysts with high molecular weights proteins [2]. However, it seems that two theories or speculations have prohibited scientists not to use enzymes in microwave-induced reactions. It is claimed that enzymes are intolerant to the temperature and pH alterations of the medium [3]. This means that enzymes are unable to act outside their temperature and pH ranges. Interestingly, it is also argued that the catalyzing effects of enzymes are higher than chemical agents in many instances [4]. After a careful search of the literature, many enzyme-catalyzed reactions in the microwave have been identified that proceed even at relatively high temperatures and under radiation. It is gratifying to note that the rate acceleration of microwave-induced enzyme-mediated reactions is much higher than those observed in chemical processes under similar situations. The most important part is that reactions carried out by chemical methods produce nonchiral compounds in the absence of chiral influences. In addition, even a mild chemical reaction seems to be drastic compared to the same when the study is conducted using enzymes in a microwave oven. Very interestingly, microwave-induced enzymatic reactions even proceed at very low power without increasing the temperature rapidly that is normally required for microwave-assisted chemical reactions. It may prove that enzymatic reactions in a microwave oven are more sensitive to radiation than temperature. In contrast, scientists believe that chemical reactions may proceed due to a combination of both [1]. Most of the published papers indicate that the thermal situation may have more control in these types of reactions.

It is reported that microwave irradiation and enzymatic catalysis synergistically increase the rate of the reaction significantly [5]. Various studies have explained the biodegradation of toxic organic pollutants utilizing various enzymes from fungi, bacteria, and plants [6, 7]. Bioremediation is an environmentally friendly and cost-effective biotechnology that is governed by microbial enzymes. The analyses in this area add to cut down the toxicity of the pollutants and also to get useful novel products. Thus, microwave technology, together with enzymatic catalysis is a nature-friendly method with good yield of the products and low wastage of solvent [8–10]. Enzymes from diverse microorganisms are associated in the biochemical processes of a broad range of compounds assisted by microwave irradiation. However, the application of biochemical methods by microwave-induced reactions remains unexplored.

The most interesting reactions that are performed by enzymes in the microwave are documented here with reference to examples that are related to medicinally active molecules. According to our knowledge, microwave-assisted enzymatic reactions for the preparation of medicinally active compounds have not been reviewed and it is discussed in the following sections. This is not a comprehensive book chapter, thus only 20 important compounds were considered.

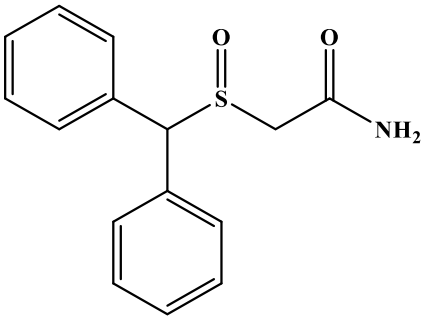

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Figure 3.1: Molecular structure of modafinil.

3.2 Lipase catalysed reactions

The hydrolysis of lipids is catalyzed by the enzyme called lipase. Because of its properties such as high biodegradability, specificity, nontoxic nature, pH dependency, high catalytic efficiency, low product inhibition, activity in organic solvents, low reaction time, high yield in a nonaqueous medium, reusability, and resistance to altered pH, temperature, alcohol, it is employed as a potent biocatalyst. Furthermore, lipase is playing a critical role in a broad range of industrial applications, like in food, detergents, textiles, leather, cosmetics, pharmaceuticals, and paper. Also, in the preparation of organic compounds, functionalization reaction, polymer synthesis, hydrolysis, transformations reaction, oxidations and epoxidation reaction, transesterification, and esterification reaction, lipase can do an important role. Synthesis of medicinally active compounds using lipases is discussed in the following sections.

Modafinil is considered as a CNS stimulant drug. This drug is applied to treat narcolepsy and hypersomnia successfully with fewer adverse effects [11]. The chemical structure of Modafinil is depicted in Figure 3.1. Several methods are reported for the synthesis of Modafinil. However, chemical procedures used for the synthesis of modafinil were not environmentally friendly and produced a huge quantity of waste. Besides, most methods utilized very risky chemicals, like chloroacetic acid, bromodiphenylmethane, thiourea, and thionyl chloride. These reactions required high temperatures and various separation stages [12].

The n-butyl diphenyl methyl mercapto acetate is one of the crucial intermediates in the biotransformation process for the synthesis of modafinil. The microwave-induced synthesis of diphenyl methyl mercapto butyrate using various lipases was reported [13]. Figure 3.2 shows the esterification reaction between n-butanol and diphenyl methyl mercapto acid for the synthesis of n-butyl diphenyl methyl mercapto acetate catalyzed by immobilized lipases**.** To find the optimized reaction conditions, different parameters like reactants mole ratio, catalyst loading, the temperature of the reaction, various lipases (Lipozyme TL IM, Lipozyme RM IM, and Novozym 435), the concentration of water, and catalysts' reusability were viewed. Among the Novozym 435 lipase was

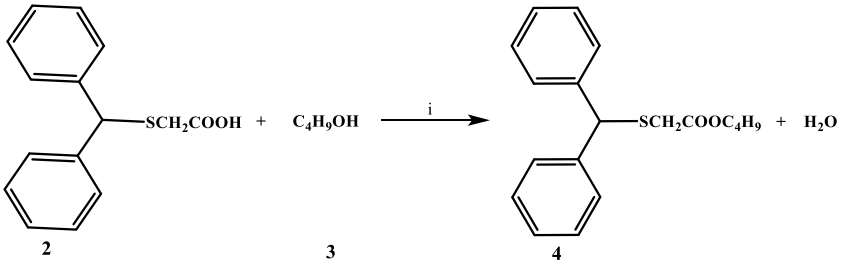

Figure 3.2: Enzyme catalyzed microwave-induced synthesis of n-butyl diphenyl methyl mercapto acetate. Reagents and conditions: (i) Lipase, MW.

observed to be the more active compared to other lipases under the influence of microwave irradiation. Under this condition with toluene as the solvent, yielded a conversion of 34% at 60 °C in 24 h. After the synthetic reaction, the enzyme was recyclable and reusable.

The comparison of enzymatic esterification reactions performed at various temperatures under microwave irradiation and conventional heating was conducted. The results showed that under microwave irradiation the overall reaction rate and conversion were much higher. For instance, it was found that, with a raise in the temperature from 40 to 60 °C, in the microwave, the reaction rate was increased from 0.0013 to 0.0021 mol/h. Under normal heating, the reaction rate was raised from 0.001 to 0.0013 mol/h only. This analysis showed that at low temperatures, the reaction rate increases with temperature and it is in accordance with the Arrhenius model. Besides, it was also evidenced that the effect may not be only effect from thermal. No conversion was observed under controlled analysis without the use of an enzyme (Novozym 435). In the absence of the enzyme, microwave irradiation failed to initiate the reaction.

The activation energy values were 8.9 and 7.9 kcal/mol, respectively, for microwave heating and conventional heating. The reaction rate enhancement was mainly because of the higher entropy or higher frequency of collision during activation by microwave. The frequency factor in the Arrhenius equation can also be altered by microwave irradiation.

Ketorolac is a nonsteroidal analgesic and anti-inflammatory drug, having one stereogenic carbon center [14]. Figure 3.3 shows the molecular structure. Studies demonstrated that the efficacy of single-dose ketorolac is higher than that of several anti-inflammatory drugs including indomethacin, aspirin, naproxen, meperidine, ibuprofen, pentazocine, and morphine [15, 16]. In that way, ketorolac has attained substantial therapeutic impressiveness. Considering the ketorolac enantiomer, the (R)-isomer is not active and exhibits adverse side effects, at the same time the (S)-isomer is observed to be very active therapeutically [17]. Therefore, the preparation of (S)-isomer is crucial. For the stereoselective synthesis of (S)-isomer, various methods are available such as esterification in organic media catalyzed by microorganisms or

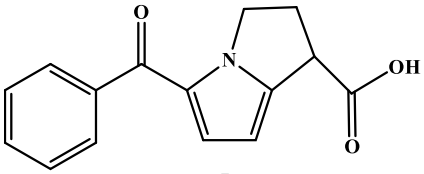

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Figure 3.3: Molecular structure of ketorolac.

enzymes, or hydrolysis in aqueous media [17–20]. However, to obtain the wanted enantiomeric excess form of ketorolac, a longer reaction time is needed for enzymatic biotransformation.

For chiral drug resolution, microwave-induced biocatalytic transformation is a green and important method. The synergistic effect of microwave irradiation was investigated in the kinetic resolution of RS-(±)-ketorolac using a lipase enzyme via esterification reaction [21]. Various immobilized enzymes (Lipozyme TL IM, Novozym 435, Lipozyme RM IM, Lipase AYS amino, and Lipase Amano AS) were considered for the kinetic resolution of RS-(±)-ketorolac under microwave conditions. Along with that, the effects of various other growth parameters like the agitation speed, different solvents, temperature, the concentration of catalyst and substrate were also viewed. Compared to conventional methods, a raise in initial rates were observed under microwave conditions. Novozym 435 lipase enzyme-catalyzed efficaciously the enantioselective esterification of RS-(±)-ketorolac in comparison with other lipases. The schematics of the reaction are shown in Figure 3.4. An enantiomeric excess >99% and a conversion of 50% were attained at 50 °C in 3 h. The study demonstrated that the Ping-Pong bi-Bi mechanism was followed by this reaction with inhibition by n-octanol.

From the Arrhenius plot, the calculated activation energies were about 9 and 10 kcal mol^{-1} under conventional and microwave heating respectively. The values were very close which suggests that the microwave irradiation made an improvement in the collision frequency. The increased reaction rate in the microwave irradiation reflected that the effect may not be only effect from thermal. The contribution of the faster reaction rate was from the microwave-absorbing nature of the reactants. The RS-(±)-ketorolac is an example of a good microwave absorbing material. Under microwave irradiation, the dipole of the RS-(±)-ketorolac may be reorienting rapidly and makes the functional unit much energetic at the interface of n-octanol and

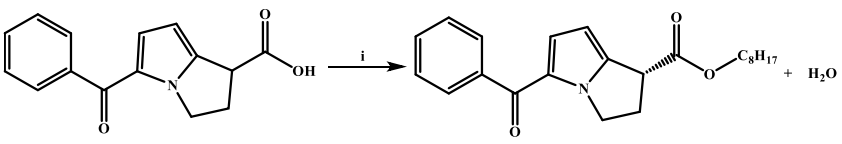

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Figure 3.4: The kinetic resolution of ketorolac induced by microwave irradiation and catalyzed by lipase. Reagents and conditions: (i) n-Octanol, Novozym 435, MWI.

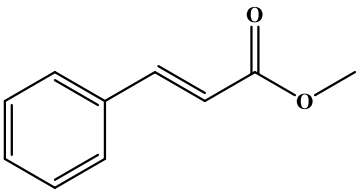

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Figure 3.5: Molecular structure of methyl cinnamate.

RS-(±)-ketorolac. Moreover, it is expected that under microwave irradiation the enzyme may act in a different manner and get much action. This is due to the conformational changes in the enzyme. It helps the substrate to access the active site of the enzyme much well than that under conventional heating.

The cinnamic acid esters are known as cinnamates. It is detected in plants to a great degree (Figure 3.5). Because of the flavor, fragrance, and antioxidant properties, these esters are used in a broad scope of applications in the pharmaceutical and food industry. Enzymatic synthesis of synthetic, semisynthetic, and natural cinnamates presents numerous advantages in comparison with chemical synthesis.

Shinde et al. investigated the microwave-assisted synthesis of geranyl cinnamate and the reaction was catalyzed by lipase enzyme [22]. Under microwave irradiation, the transesterification reaction of ethyl cinnamate for the synthesis of geranyl cinnamate is depicted in Figure 3.6.

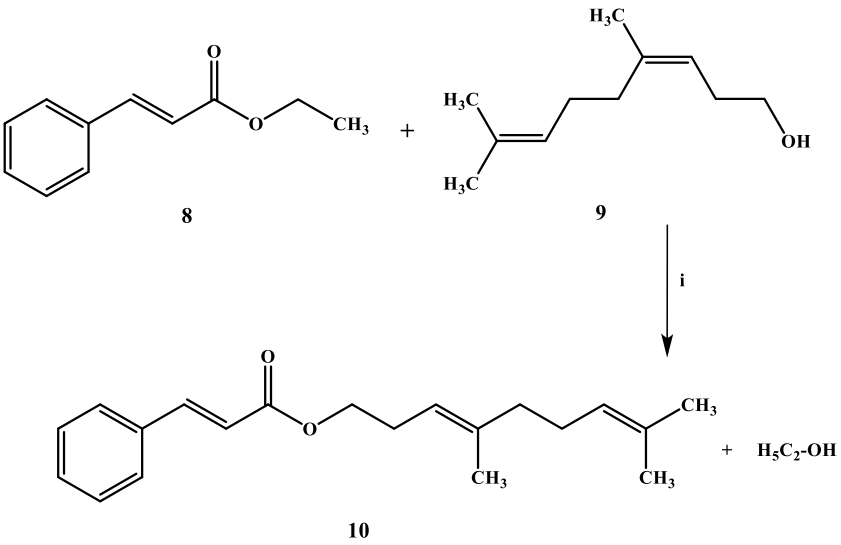

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Figure 3.6: Transesterification of ethyl cinnamate under microwave irradiation. Reagents and conditions: (i) MWI, Novozym 435.

The effects of various growth parameters like biocatalyst, temperature, and solvent were studied in detail. The lipases such as Novozym 435 (*Candida Antarctica* lipase B) Lipozyme RM IM*(Rhizomucormiehei)*, and Lipozyme TL IM (*Thermomyceslanuginosus*), were tested for the analysis. Among the three considered enzymes, the lipase Novozym 435 presented the maximum conversion. 83% of conversion was obtained with Novozym 435, 8% for Lipozyme RM IM, and a very minor conversion was observed with Lipozyme TL IM. At 60 °C, the initial rate was observed to be enhanced under both conventional and microwave heating. However, under microwave irradiation, a raise in initial rates up to about 4-fold was found in comparison with the conventional method.

The molecular structure of a triolein (glyceryl trioleate) is shown in Figure 3.7, it is a symmetrical triglyceride. It can be synthesized using three sets of unsaturated fatty acid oleic acid and glycerol. Triolein is the major substance of olive oil [24] and is one of the two constituents of Lorenzo's oil [23]. It acts as a *Caenorhabditis elegans* as well as plant metabolite. For the synthesis of glycerol and fatty acid, hydrolysis of triglyceride is a convenient and important procedure. They are employed in a broad range of applications in the field of pharmaceuticals, nutrients, emulsifiers, and so on.

The triolein hydrolysis was reported by several researchers. Considering the methods, for the production of fatty acids enzymatic hydrolysis is a practicable procedure [25–28]. The mechanistic pathway for the hydrolysis of triolein by lipase (*Candida rugosa*) in the water-biphasic oil arrangement was also studied substantially [29]. With microwave application, an improvement in the rate of reaction was detected.

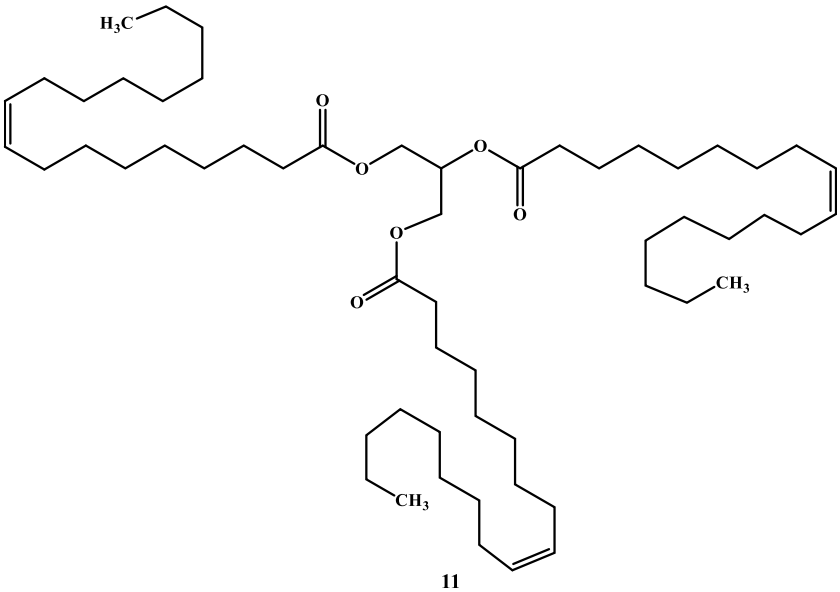

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Figure 3.7: Molecular structure of triolein.

The microwave heating effect on the hydrolysis of triolein catalyzed by lipase enzyme was investigated by Chena et al. [30]. The study was targeted to find whether the rate of reaction improvement was entire as a result of non-thermal effects or heating/thermal effects. For this purpose, both the conventional heating and microwave-assisted methods were viewed. To take a precise kinetic analysis of the enzyme-catalyzed triolein hydrolysis, spectroscopic analysis was considered. Commercial lipases from *Burkholderiacepacia*, *Porcine Pancreas,* and *Candidarugosa* were used for the study. When the hydrolysis of triolein was performed at the same temperature, no significant differences in the product yield were found between conventional and microwave heating methods. The analysis evidenced that lipases from *Candidarugosa* had optimum catalytic action at 37 °C, at the same time the other two enzymes performed well at 50 °C. The study also described that in the case of microwave-induced lipase hydrolysis of triolein, only the thermal effect exists. Therefore, higher temperature conventional heating, for instance at 50 °C temperature, can also be employed to speed up the hydrolysis. This study also confirmed that enzymatic reactions can be conducted at a relatively high temperature.

Isoamyl butyrate is the butanoate ester of isoamylol, it is also named isopentyl butanoate and the molecular structure is shown in Figure 3.8. This compound has a role of a metabolite and belongs to the class of fatty acid esters. It also functions as a flavoring agent and is used in the preparation of different fruit juice flavors. Besides, it is widely used in the cosmetic, pharmaceutical, beverage, and food industries as a fragrance and flavor compound. This compound is normally prepared by esterification of isoamyl alcohol and butyrate using lipase as the catalyst. Under microwave conditions, the enzymatic synthesis of isoamyl butyrate is also possible.

During the enzymatic synthesis of isoamyl butyrate ester in a solvent-free system, the effect of microwave irradiation was investigated by Bansode et al. [31]. To optimize the reaction conditions under the solvent-free to obtain the maximum yield, different parameters were analyzed. About 95% conversion was found at 60 °C in 120 min using 700 W microwave power. The thermodynamic data of the reaction were also studied and compared with the data obtained from the conventional and ultrasonic methods. Because of the lower activation energy associated with the microwave system, an enhancement in the reaction rate was noticed in the microwave method. Thus, compared to the ultrasonic method and conventional method, the lipase-catalyzed solvent-free esterification was intensified 1.5 to 5-fold using microwave energy. In contrast, with temperature raise from 60 °C to 70 °C, a decrease in conversion from 95 to

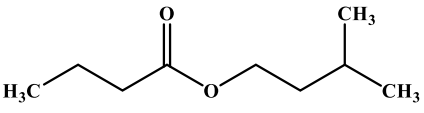

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Figure 3.8: Molecular structure of isoamyl butyrate.

83% was observed, which was due to the thermal denaturation of the enzyme. This study had reflected the critical role of enzymes on temperature.

The organic compound ethyl valerate is used in flavors, it is also known as ethyl pentanoate. It also has other applications in the food, biofuels, pharmaceutical, and cosmetics industries. For the synthesis of ethyl valerate, various synthetic methods are available. The molecular structure of ethyl valerate is depicted in Figure 3.9.

Microwave-assisted solvent-free enzymatic synthesis route using ethanol and valeric acid was also investigated [32]. Three lipases, namely, Lipozyme TL IM, Novozyme 435, and Lipozyme RM IM were considered for the synthesis. The enzyme Novozym 435A produced a better result. A 69.2% of valeric acid conversion in 40 min was reported at 50 °C under microwave irradiation with an enzyme loading of 10 gL^{-1}. The schematics of the reaction are shown in Figure 3.10. The other two enzymes produced only a very little conversion.

In the synthesis of n-butylpropionate under conventional and microwave heating in solvent-free conditions, temperature plays a critical role. Under microwave heating, the reaction rate and conversion were higher in comparison with conventional heating. This was because of the enzymatic actions, ionic, polar characteristics of the reaction mixture, and microwave absorption property.

Lactate esters are derivatives of lactic acid [88]. Lactate esters are used in a broad range of applications. For example, in the production or composition of multitude products, such as paints, packaging, cleansers, grease removers, copolymers of biodegradable plastics, glycol, and acrylates. Among the lactate esters, ethyl lactate (lactic acid ethyl ester, ethyl 2-hydroxypropanoate) is reported as a monobasic ester that is synthesized using ethanol and lactic acid. It is a natural flavoring agent, hence a worthful perfumery and food additive [89]. Ethyl lactate is one of the most common solvents in cosmetics, pharmaceuticals, coatings, detergents, fragrances, and food production. The molecular structure of ethyl lactate is shown in Figure 3.11.

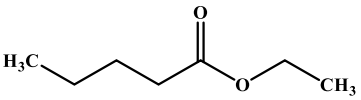

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Figure 3.9: Molecular structure of ethyl valerate.

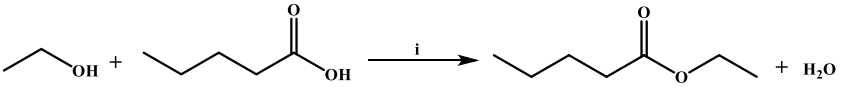

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Figure 3.10: Microwave-assisted solvent-free enzymatic synthesis of ethyl valerate using ethanol and valeric acid. Reagents and conditions: (i) MWI, Novozym 435, 50 W, 50 °C.

Lactic acid and ethanol esterification are important for the synthesis of ethyl lactate. On the enzyme-catalyzed esterification of lactic acid, microwave heating was observed to have a beneficial effect. Major et al. investigated the effect of microwave radiation on the enzymatic synthesis of ethyl lactate in an ionic liquid medium [90]. To determine an appropriate medium for the synthesis of ethyl lactate several ionic liquids were tested. The study reported that as Cyphos 202 and Cyphos 104 consist of the same cation with different anions, the reaction could be accomplished in it. It was reported that microwave irradiation heightened the production of ethyl lactate and speeded up the lactoyllactic acid hydrolysis (the linear dimer of lactic acid). Combination microwave irradiation with the esterification in the extracting agent as co-solvent resulted in synthesis with increased rate and yields.

Poly-ε-caprolactone (PCL) is a biodegradable polyester. It is also employed for modelling, splinting, as a raw material for prototyping systems and for the production of special polyurethanes. It is also used as implantable biomaterial, a device for drug delivery, and adhesion or barrier suture, [91]. The synthesis of PCL has been investigated in a widespread way [92–95]. Microwave-induced solvent-free enzymatic synthesis of PCL was also reported [96]. The ring-opening polymerization of ε-caprolactone is shown in Figure 3.12.

The growth parameters such as microwave intensity, reaction time, and temperature were tested. Under optimal conditions, the polymerization reaction resulted in poly-ε-caprolactone with a polydispersity index of 1.2 and Mn of 20,624. The results also showed a positive response on the properties of poly-ε-caprolactone by temperature, and high microwave irradiation was not suitable. Caprolactone absorbs

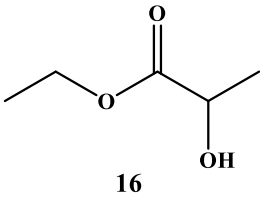

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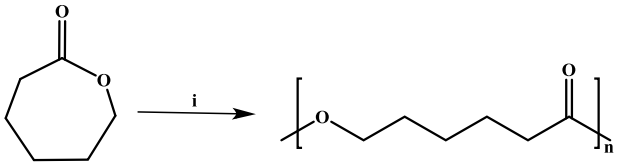
Figure 3.11: Molecular structure of ethyl lactate.



17 18

Figure 3.12: Ring-opening polymerization of ε-caprolactone assisted by microwave. Reagents and conditions: (i) MWI, Lipase.

microwave energy very efficaciously. Due to the increase in the bulk temperature, the raise in power resulted in a greater instantaneous microenvironment temperature in the chemical reaction. It affected the enzyme and its microenvironment and resulted in enzyme activity loss [97].

Amines with a neighboring enantiomerically pure chiral center have lots of applications. In the agrochemical and pharmaceutical industries, they are important for the synthesis of biologically active compounds [98]. For the resolution of chiral amines, acetylation catalyzed by the enzyme is one of the important and fastest techniques [99]. Hydrolytic enzymes like lipase are widely employed for this purpose because of their stability, broad substrate specificities, and non-necessity for cofactors [100, 101].

Sontakke et al. reported microwave-assisted kinetic resolution of (±)-1-phenylethylamine with ethyl acetate as an acyl donor using lipase as catalyst [102]. The schematic of the reaction is depicted in Figure 3.13. At 45 °C, the resolution of (±)-1-phenylethylamine using Novozyme 435 as catalyst was tested using both microwave and conventional heating. In microwave heating, after 4 h the conversion increased up to 49%, while in conventional heating, after 10 h the conversion was only up to 35%. A substantial increase in the rate of the reaction and optical purity were observed with the microwave method in comparison with the conventional method. During microwave irradiation, the functional groups, that possess dipole rotational effect or ionic conductivity, absorb the energy. The functional group's reactivity with encircled reactants increases due to this absorption compared to simple incubation at a similar temperature condition. It was described that microwave heating increased the lipase-catalyzed reaction rate by around 2–5 times. Because of the wave–material interactions, the trace of residual water staying in the enzyme beads normally heated quickly. This led to thermal effects which are related to charge space polarization and dipolar and specific which is purely nonthermal. The enzyme activity was improved by these effects. The flow of heat and thermal gradients were observed to be the opposite of those in materials that get heated by conventional heating methods, which is generally the cause for the enhanced selectivity and activity. This evidenced that, a synergistic effect was produced by microwave irradiation together with lipase catalysis.

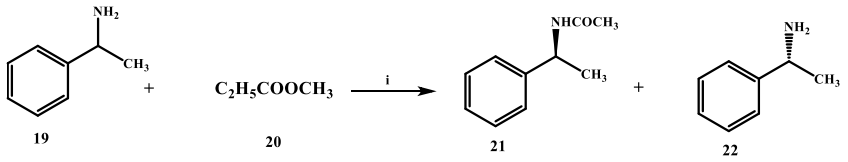


Figure 3.13: Microwave-assisted enzyme-catalyzed resolution of (RS)-1-phenylethylamine. Reagents and conditions: (i) Novozym 435, MTBE, MW.

Styrene oxide is an efficient and important intermediate for the preparation of organic compounds. Both *in situ* and *ex situ*, the lipases catalyzed epoxidation of styrene-to-styrene oxide at 55 °C using perlauric acid as the oxidizing agent were studied under both microwave and conventional heating [103]. The chemoenzymatic styrene oxide epoxidation is shown in Figure 3.14. In the first step, from hydrogen peroxide and lauric acid production of perlauric acid was occurred in the presence of lipase (*Candida antarctica*). To produce styrene oxide, the synthesized perlauric acid was then reacted at the same instant with styrene. Studies showed that hydrogen peroxide deactivates the enzyme [104], thus special emphasis using microwave irradiation was considered to enhance the activity and stability of the enzyme.

The microwave effect on the generation of perlauric acid is shown in Figure 3.15. It was observed that under microwave irradiation both the reaction rate as well as the overall conversion were more compared to the conventional method, showing that the effect may not be only effect from thermal. Besides, during the epoxidation of styrene, it was observed that the reaction rate and the overall conversion were more under microwave heating in comparison with the conventional method.

Esters of adipic acid are important compounds. For example, adipic acid monoesters are especially employed in regioselective transformations, in Kolbe reaction [105, 106], and also as a structural unit for chiral building block, [107]. On the other hand, diesters are widely used as lubricants and as precursors in biodegradable polymer synthesis [108]. Generally, esters are synthesized in the presence of an acid catalyst using a dibasic carboxylic acid and alcohol. Several heterogeneous catalysts such as activated clay, cation-exchange resins, modified heteropoly acids and zeolites, and homogeneous catalysts such as hydrochloric acid, sulfuric acid, methanesulfonic acid, and *p*-toluene sulfonic acid were used for the synthesis [109–112]. Enzymatic syntheses of adipic acid esters were also reported [113, 114]. The enzymatic preparation of adipic acid di and monoesters under microwave irradiation in nonaqueous media was reported [115].

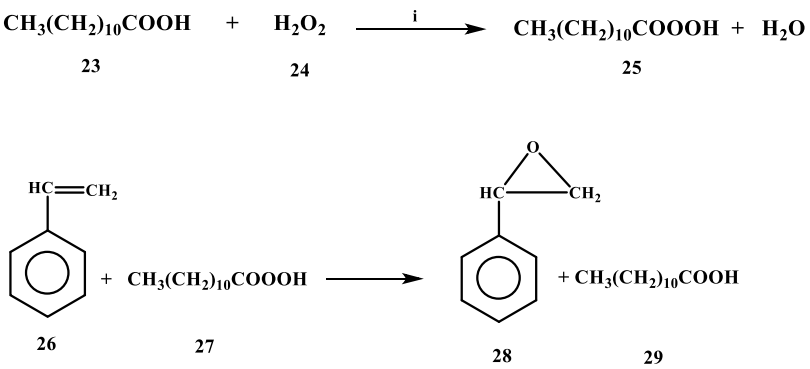


Figure 3.14: Lipase-catalyzed styrene oxide synthesis. Reagents and conditions: (i) Lipase.

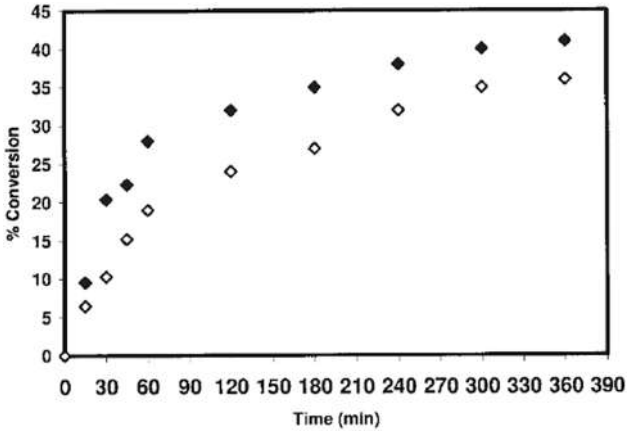


Figure 3.15: Microwave effect on the generation of perlauric acid. (◊) conventional and (◆) microwave. Adapted with permission from [103].

At a controlled temperature of 60 °C, different alcohols were tested with adipic acid in the presence of lipase enzyme employing both conventional heating and microwave heating (Figure 3.16). Under microwave irradiation, overall conversion and reaction rates were higher in comparison with the conventional heating method. This demonstrates that the effect may not be the only effect from thermal.

Fatty acids monoesters with glycerol have a broad spectrum of usages such as in pharmaceuticals, food industries, and cosmetics. For instance, very effective emulsifiers can be prepared using the propylene glycol esters of respective aliphatic acids. The propanediol ester of lauric acid is mainly used as an emollient and emulsifier in the preparation of pharmaceuticals [116, 117]. The propylene glycol monoesters synthesis using chemical procedures requires high temperature and pressure. The chemical methods are mainly based on base-or acid-catalyzed propylene glycol esterification with fatty acids. This method generally leads to a product with low purity. Yadav et al. reported the microwave-assisted enzyme-catalyzed propylene glycol esterification with lauric acid in non-aqueous media for the preparation of propylene glycol monolaurate [118]. The reaction scheme is shown in Figure 3.17.

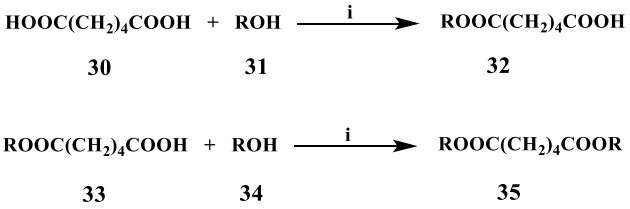


Figure 3.16: Adipic acid esterification with various alcohols. Reagents and conditions: (i) Lipase, MW.

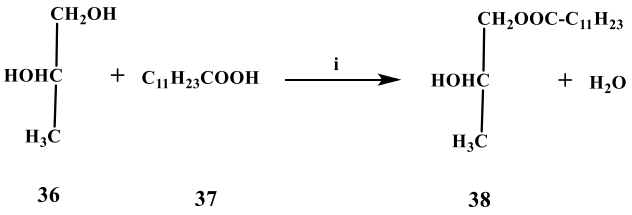


Figure 3.17: Propylene glycol esterification with lauric acid. Reagents and conditions: (i) Lipase, MW.

Various lipases, such as PS-C "Amano", Lipozyme RM IM, Novozym 435, and Lipozyme TL IM were considered for the reaction. With Novozym 435 lipase a conversion of 48% was obtained in 3 h and found to be the most effective catalyst among them. Lipase PS-C "Amano", Lipozyme TL IM, and Lipozyme RM IM produced only conversions of 0, 7, and 11% in 3 h, respectively.

In microwave heating, a raise in the temperature in the range of 30–60 °C, increased the initial reaction rate in the range 0.02–0.06 mol/(l-min-g-enz). In contrast, when the temperature was increased to 70 °C the rate of reaction was decreased to 0.045 mol/(l-min-g-enz). However, the rate of reaction was raised from 0.02 to 0.05 mol/(l-min-g-enz) with the increment in the temperature (30–60 °C) in the case of conventional heating. Like microwave heating, an additional raise in the temperature (at 70 °C) decreased the reaction rate to 0.045 mol/(l-min-g-enz). At 60 °C, the improvement in the rate of reaction due to the microwave method over the conventional method was nearly 33%. It is crucial to mention that 35 W microwave power was enough to make such an increment in the reaction rate. Following the Arrhenius model, the reaction rate was increased with the rise of temperature at 35 W power. Because of the extensive irreversible lipase denaturation, this model collapses at a higher temperature.

Isoniazid (isonicotinic acid hydrazide) is an antibacterial drug, mainly used for the treatment of tuberculosis. It was prepared first in 1912 and the anti-tuberculosis activity of the compound was identified in 1952. This drug is widely employed in combination therapy with ethambutol and rifampicin. Chemically isoniazid is prepared in the presence of sodium hydroxide from hydrazine hydrate and 4-cyanopyridine under reflux conditions for 7 h at 100 °C [119]. Another method is using hydrazine hydrate and ethyl isonicotinate [120]. Enzymatic preparation of isoniazid employing immobilized lipase enzyme was also reported [121]. The enzymatic synthesis of isoniazid using ethyl isonicotinate and hydrazine hydrate in non-aqueous media under both microwave and conventional heating was investigated [122]. The schematic of the reaction is shown in Figure 3.18.

Three distinct lipases were considered, namely Lipozyme TL IM, Lipozyme RM IM, and Novozym 435. Among them, the lipase Novozym 435 was observed to be the more active. Under microwave irradiation, the final conversion, as well as rate of reaction, enhanced synergistically in comparison with the conventional method (Figure 3.19).

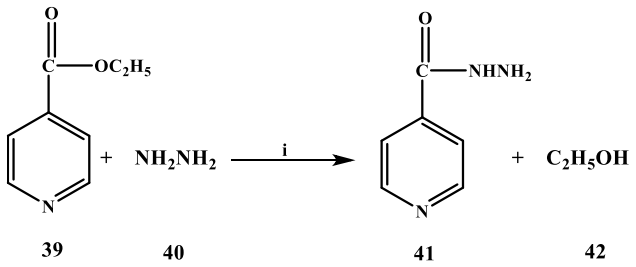


Figure 3.18: Enzymatic synthesis of isoniazid. Reagents and conditions: (i) Lipase, MW.

Mandelic acid enantiomers are one of the crucial chiral analogues that are mainly utilized for the resolution of racemic amines and alcohols [123–125]. For the synthesis of various pharmaceuticals including semi-synthetic cephalosporins and penicillins, the R-(-)-Mandelic acid is practicable [123, 126, 127]. Besides, it is also applied in the treatment and prevention of honeybee diseases, for toxoplasmosis, and in agro-chemical synthesis. Various synthetic routes are available for the preparation of R-(–)-mandelic acid including the hydrolysis using mandelic acid derivatives with microorganisms [128, 129], racemic mandelic acid oxidation with microorganisms [130], 1-phenyl-1,2-ethanediol oxidation with microorganisms [131], asymmetric reduction of benzoylformic acid with microorganisms [132], and asymmetric enzymatic preparation using n-keto aldehyde [133]. The microwave-assisted resolution of RS-(±)-methyl mandelate *via* lipase-catalyzed hydrolysis in non-aqueous media to make R-(–)-mandelic acid was also investigated [134]. Figure 3.20 shows the schematics of the reaction.

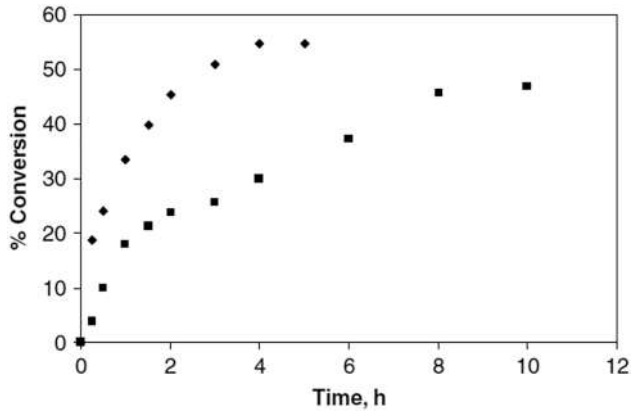


Figure 3.19: Reaction rate and conversion. (■), conventional; (◆), microwave. Adapted with permission from [122].

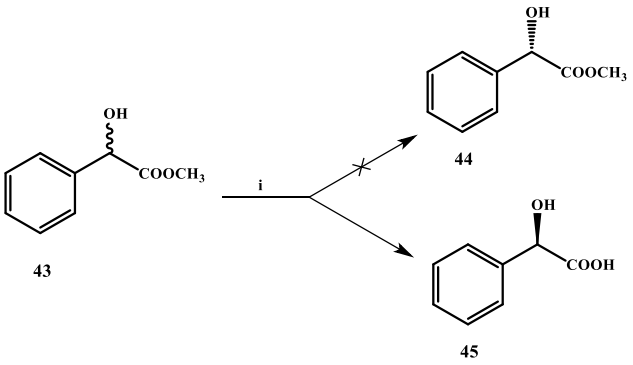


Figure 3.20: Resolution of RS-(±)-methyl mandelate. Reagents and conditions: (i) MWI, Novozym 435, water, 50 °C.

Among three enzymes, the Novozym 435 lipase was observed to be the more active for the R-(–)-methyl mandelate hydrolysis in tert-butanol as a solvent at 50 °C. The product was obtained after 4 h with an optical purity of 84.2%. High stereoselectivity for the R-(–)-enantiomer was observed with the enzyme and left the S-(+)-enantiomer unhydrolyzed.

Fatty acids are the major plentiful constituent of oils [135]. Fatty acid methyl esters is normally synthesized by transesterification of fats using methanol. Vegetable oils possess antibacterial and antifungal activities, these properties being particularly due to the existence of fatty acids [136, 137]. Studies also showed the potential methyl esters as antifungals and antioxidants [138–143]. Besides, they are also utilized to make biodiesel and detergents and as biomarkers to identify groups of microorganisms. Yu et al. reported the microwave-assisted production of fatty acid methyl esters by transesterification of soybean oil with methanol using lipase enzyme [144]. A schematic of the synthesis of fatty acid methyl ester is shown in Figure 3.21.

The activity of the enzyme was raised in the transesterification reaction under microwave irradiation. In the first 4 h, the rate of reaction bettered up to 1.5-fold in comparison with the conventional method. The microwave-induced transesterification

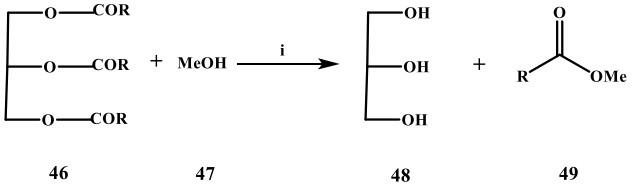


Figure 3.21: Microwave-assisted enzymatic synthesis of fatty acid methyl ester. Reagents and conditions: (i) Novozym 435, MWI.

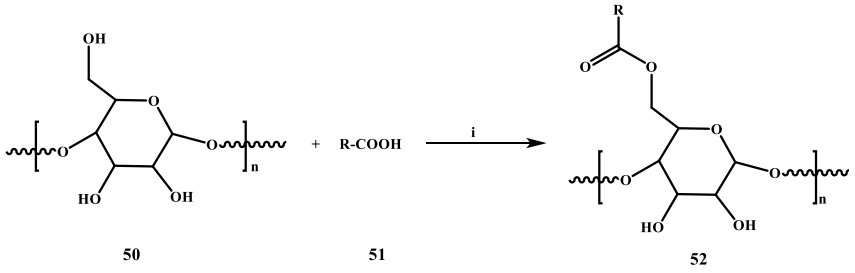
was also attained an equivalent product yield in a comparatively short time compared to that of the conventional method.

Starch is one of the most extensively applied pharmaceutical excipients. It meets most of the requirements for excipients with minimal processing. Besides, it is non-toxic, inexpensive, odorless, widely available, and biocompatible. Modified starch is used in a range of areas. For example, it is used as hot melt adhesives, tablet binders, cigarette filters, coating, pharmaceutical aspects, and packaging materials [147–150]. Different esterification methods such as chemical techniques, enzymatic techniques, and physical techniques to supply altered starches of good quality were reported [151–155].

By employing both low-power microwaves and biocatalysis a method for esterification of starch was reported [156]. Employing microwave-induced enzymatic transformation of starch, plenty of starch esters were produced. In this method, hog pancreas lipase was applied as a biocatalyst. As reaction media, DMSO and DMF were used (Figure 3.22). Low power microwave radiation was applied in the reaction mixture and compared the results with the conventional heating method. The analysis demonstrated that the microwave-assisted esterification in DMF and lauric acid as an acyl donor produced the highest degree of substitution (around 0.51). Besides, a reduction in the reaction time (2.5 times) was observed with for microwave method. The method was practicable for producing starch ester with higher efficiency.

3.3 Cellulase catalysed reactions

Cellulolysis is the decomposition of cellulose and related polysaccharides. Cellulolysis is catalyzed by cellulase-containing enzymes and the cellulase generally hydrolyzes β-1,4-glucoside linkages of the cellulose chain. The enzyme is mainly produced by bacteria, protozoans, and fungi. Different types of cellulases are available; they differ mostly mechanistically and structurally. In the food processing, textile industry,



50 51 52

R=CH_3, $C_{11}H_{23}$, $C_{17}H_{35}$

Figure 3.22: Microwave-assisted esterification of starch. Reagents and conditions: (i) MWI, lipase, DMSO/DMF.

brewery and wine, laundry detergents, pulp and paper industries, animal feed industries, agriculture, and pharmaceutical industries, cellulases are used to a great degree. The cellulose activity changes due to microwave irradiation are discussed below.

Astragalus polysaccharide is a water-soluble heteropolysaccharide and it has a bioactive effect (Figure 3.23). From *Astragali Radix* (the dry root of *Astragalusmembranaceus*), astragalus polysaccharide can be extracted. This polysaccharide is having medicinal activities such as anti-ageing, antitumor, immunomodulation, antioxidant, antiviral, cardiovascular protection, and anti-inflammatory activities [33–35]. The major constituents of astragalus polysaccharides are galactose, glucose, rhamnose, xylose, arabinose, mannose, galacturonic acid, and glucuronic acid. As the structure and chemical composition of astragalus polysaccharides play a key role in biological activities, the extraction of astragalus polysaccharides is important. Several extraction methods are reported for astragalus polysaccharide preparation [36–44].

To extract astragalus polysaccharides, cellulose hydrolysis by the microwave-assisted method was also studied [45]. At optimized enzymatic-microwave conditions, a maximum extraction rate of about 16% and a purity of about 88% were found and the values were greater than those obtained by other methods. For the extraction of astragalus polysaccharides from *Astragali Radix*, the microwave-assisted enzyme-catalyzed technique is an efficient and faster method.

3.4 Glycosidases catalysed reactions

For carbohydrate metabolism, glycosidases are crucial enzymes. The *in vivo* of oligo- and polysaccharides degradation is the main responsibility of these enzymes. The glycosidic bond's hydrolysis in carbohydrates and other related compounds is

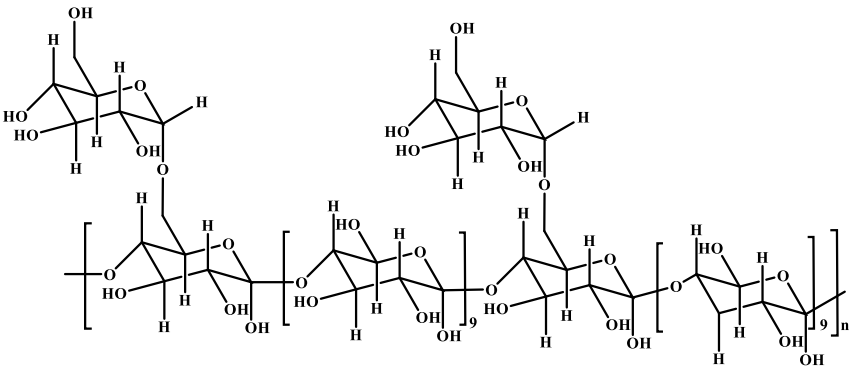


Figure 3.23: The repeating unit of astragalus polysaccharide.

catalyzed by glycosidases. They are also participating in other actions, it includes biomass degradation, anti-bacterial defense strategies, intestinal digestion, pathogenesis mechanisms, glycoproteins posttranslational modification, normal cellular function, and lysosomal catabolism of glycoconjugates.

Several of the biologically active compounds are glycosides. It involves glycosides of vitamins, alkaloid glycosides, polyphenolic glycosides (flavonoids), cardiac glycosides, glycosides in the group of antibiotics, glycopeptides, steroid, and terpenoid glycosides. Besides, glycosides extracted from different medicinal plants showed anticancer activity against various cancers [145]. There are several ways to synthesize glycosidic bonds chemically. Glycosidase catalyzed microwave-assisted reversed hydrolysis and transglycosidations in dry media was investigated (Figure 3.24) [146].

In many biochemical reactions, oligosaccharides and its derivatives play a critical role. Oligosaccharides and its derivatives are widely used in several applications such as in therapeutic, cosmetics, food industry, and diagnostic tools [46]. The growth of Bifidobacteria in the human body is stimulated by a derivative of an oligosaccharide called galacto-oligosaccharides [47–49]. Galacto-oligosaccharides are also recognized as a Bifidus growth factor. In humans, to maintain intestinal balance, for antitumorigenic activity, to improve the lactose tolerance and milk products digestibility, to reduce serum cholesterol levels, to enhance dietary calcium absorption, and to synthesize B-complex vitamins, the intestinal Bifidobacteria are needed [50]. Because of this, galacto-oligosaccharides synthesis is crucial. For the synthesis of oligosaccharides, various methods are reported [51–55]. However, chemical synthesis needs long protection deprotection steps to control selectivity, makes unwanted enantiomers, and usually produces low yields and mainly very complicated procedures [56]. A promising alternative is the enzymatic synthesis method.

From lactose, galacto-oligosaccharides can be prepared under microwave irradiation by using β-galactosidase from *Kluyveromyceslactis* [57]. The synthesis was executed under microwave irradiation in phosphate buffer supplemented with $MgCl_2$, lactose, and immobilized β-galactosidase (Figure 3.25). The reactions were performed till the lactose depletion happen and stopped by heating for 10 min at 100 °C. The

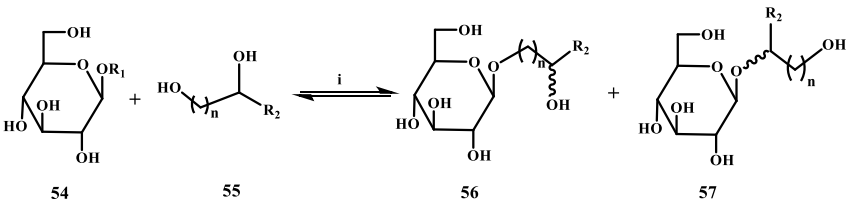


Figure 3.24: Microwave-assisted transglycosylations catalyzed by glycosidases. Reagents and conditions: (i) MWI, glycosidase support.

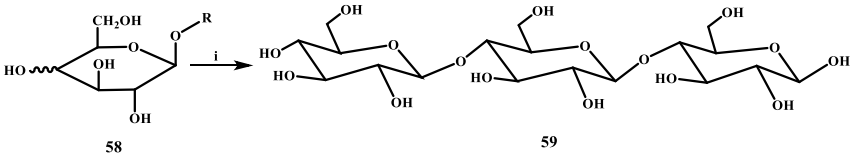


Figure 3.25: Microwave-assisted transglycosylation of lactose using galactosidase. Reagents and conditions: (i) MWI, β-galactosidase.

selectivity of galacto-oligosaccharides was raised by enhancing the initial concentration of lactose, minifying the water activity of media, and employing co-solvents in the media. Compared to the conventional method, the galacto-oligosaccharides selectivity was raised 217-fold with the addition of co-solvents (for example hexanol) and by disclosing immobilized enzyme to microwave irradiation.

The microwave-assisted preparation of nucleotide-activated oligosaccharides by transglycosylation using galactosidase from *Bacillus circulans* was studied [58]. The synthesis pathway is depicted in Figure 3.26.

The action by which covalent attachment of saccharides to lipids and proteins or other molecules is known as glycosylation. Glycosylation is an enzyme-guided location-specific action. Both the deglycosylation and glycosylation process works a key role in protein stabilization [60], protein folding [59], protein, and cellular trafficking [61], quaternary structure [63], and protease protection [62]. Glycosylation also has important effects on inflammation, receptor binding, and disease recovery [64–67].

For deglycosylation, the commonly used and standard method is overnight digestion with the corresponding deglycosylating chemicals or enzymes. Several

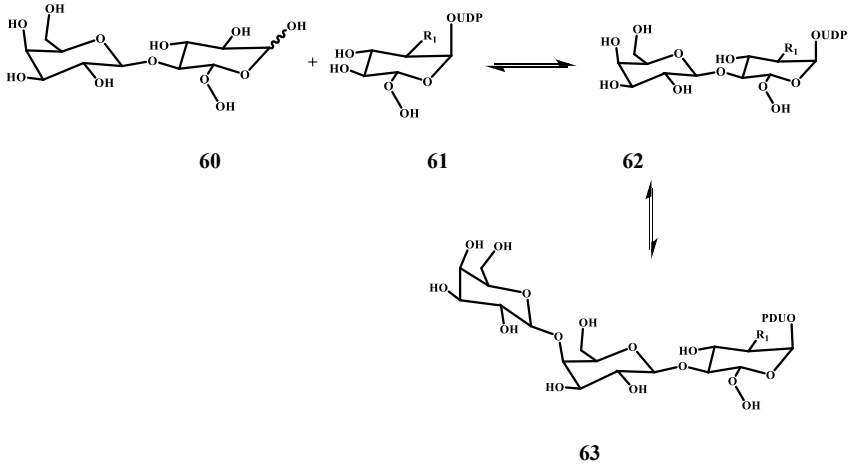


Figure 3.26: Transglycosylation for the synthesis of UDP-Lac(NAc) using β-galactosidase.

techniques were reported to improve this method, it includes deglycosylation utilizing hydrophilic and hydrophobic chip technology [69], optimization of reaction conditions employing anhydrous trifluoromethane sulfonic acid [68], glycosylated protein's PVDF-immobilization accompanied by incubation using a deglycosylating enzyme [70], for facile immobilization on cellulose the engineering of hybrid deglycosylation enzymes [72] and with enzyme peptide N-glycosidase F the incubation of glycoproteins in the presence of surfactants [71].

Microwave-assisted method for the accelerated removal of N-linked oligosaccharides using peptide N-glycosidase F enzyme was investigated [73]. Without compromising the integrity of protein samples, complete deglycosylation was attained within 30 min for the majority of protein samples. The microwave-assisted enzymatic method was significantly faster compared to conventional deglycosylation methods. On a variety of glycoproteins, this method was examined. No damaging effects such as deamidation, poor recovery, or protein backbone cleavage were reported.

3.5 Yeast catalysed reactions

Hundreds of species are identified in the yeast family. One of the most renowned species of yeast is *Saccharomyces cerevisiae* and it is commonly called Baker's or brewer's yeast. For several biotechnological applications, Baker's yeast is widely employed. Depending on the moisture substances, Baker's yeast is available in various forms. It can also be used in the synthesis of organic compounds. For example, it is employed in several reactions as a biocatalyst. The reactions include condensation, oxidation, reduction, hydrogenation, cyclization, and hydrolysis. The baker's yeast is employed in two forms (free form and immobilized form) during different reactions. To synthesize ethanol via fermentation, Baker's yeast is also practicable. Because of microwave effects, the variations in the baker's yeast activity are described in the following sections.

Trehalose is a nonreducing disaccharide. Trehalose comprises two alpha, alpha-connected glucose moieties as shown in Figure 3.27. It is considered to be the glucose storehouse. It is not present in vertebrates and is detected in different other organisms such as fungi, bacteria, insects, yeast, and plants.

Besides reservation of glucose trehalose has several other functions like protection of membranes and proteins against stresses such as high osmolarity, desiccation, heat, and frost; functioning as a crucial element of mycobacterial cell walls and a mycolic acid donor, and work as a transcriptional regulator and allosteric inhibitor in glucose metabolism. This molecule is considered as the preservative of practical importance, as it is used to preserve diverse products that are unstable including foods, enzymes, cosmetics, and pharmaceuticals [74]. For the synthesis of this molecule, five known biosynthesis pathways are reported, however, only three are commonly used [75].

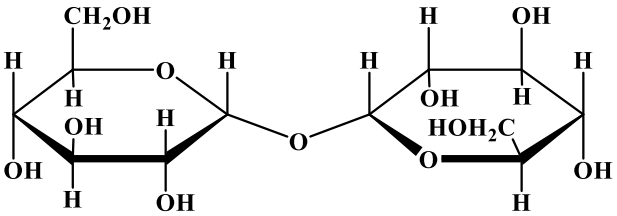


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Figure 3.27: Molecular structure of trehalose.

Corynebacteria and mycobacteria possess all three pathways, but most of the other organisms own only one pathway.

Trehalose is majorly synthesized from yeast (*Saccharomyces cerevisiae*) for large-quantity production. Trehalase is a hydrolytic enzyme of trehalose found in yeast. It was reported that trehalose extraction from the baker's yeast was controlled by the activity of trehalase [76]. Hence, before extraction, it is important to inactivate trehalase. One of the methods to inactivate trehalase is by adjusting pH, extraction temperature, and the concentration of ethanol [76]. From thermally addressed yeast, a high extraction ratio of trehalose can be accomplishable [77]. Inactivation of trehalase is possible by treating fresh *Saccharomyces cerevisiae* with microwave irradiation [78]. The yeast cell got disrupted and the trehalase enzyme became inactive after 60 s of microwave treatment. From microwave treated yeast at room temperature in 10 min by water, it was easy to extract trehalose as the yeast cell was lysed and trehalase was not active. For trehalose preparation from yeast, the microwave-assisted method is seemed to be an efficient pre-treatment method. For intracellular product preparation, the microwave-assisted method is also applicable to different materials.

β-lactams are biologically active compounds. For example, these compounds have a broad spectrum of medicinal activities, such as antibacterial [79], antifungal [80], anti-inflammatory [81], cholesterol absorption inhibitors [82], anti-hepatitis [83], antihyperglycemic [84], analgesic [85] and anticancer [86]. For example, the side chains of Taxol and Taxotere can be obtained from hydroxy-β-lactams. Taxol and Taxotere are clinically active anticancer drugs and the molecular structures are shown in Figure 3.28.

Banik et al. reported microwave-induced Baker's yeast-mediated reduction of 3-keto β-lactams to chiral 3-hydroxy derivatives [87]. Baker's yeast (*Saccharomyces cerevisiae*, type 3) was used to reduce the keto functionality of α-keto-β-lactam **1** in glycerol under microwave irradiation. Two hydroxyl compounds **2** and **3** were produced in a 3:1 ratio in a 55% yield schematic of the reaction is shown in Figure 3.29. NMR data of products **2** and **3** indicated their *cis* and *trans*-configuration. Studies of enzymatic reactions by microwave on β-lactams were not investigated. Therefore, enzymatic reactions under microwave on β-lactams should prove to be highly significant because of the diverse clinical applications of these types of molecules.

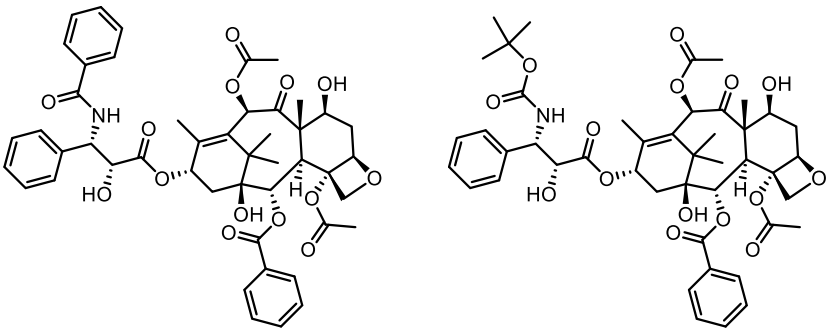

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Figure 3.28: Molecular structure of taxol and taxotere.

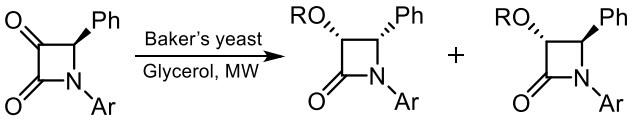

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Figure 3.29: Reduction of 3-keto β-lactams to chiral 3-hydroxy derivatives.

Table 3.1 highlights the considered biologically active compounds in this article.

Table 3.1: Summary of the investigation.

Enzyme	Biologically active compounds considered	References
Lipase	Modafinil (Conversion of 34% of substrates at 60 °C in 24 h Novozym 435)	[13]
	Ketorolac (Conversion of 50% of substrates at 50 °C in 3 h Novozym 435)	[21]
	Cinnamates (Conversion of 83% of substrates at 60 °C)	[22]
	Triolein (Hydrolysis at 50 °C)	[30]
	isoamyl butyrate (Conversion of 95% of substrates at 60 °C in 120 min)	[31]
	Ethyl valerate (Conversion of 69.2% of substrates at 50 °C in 40 min)	[32]
	Ethyl lactate	[90]
	Poly-ε-caprolactone	[96]
	Phenylethylamine (After 4 h the conversion increased up to 49%)	[102]
	Styrene oxide	[103]
	Adipic acid esters	[115]
	Propylene glycol monolaurate (Conversion of 11% of substrates in 3 h, at 60 °C)	[118]
	Isoniazid	[122]
	Mandelic acid enantiomers (Conversion occurred in 4 h, at 50 °C)	[134]

Table 3.1: (continued)

Enzyme	Biologically active compounds considered	References
	Fatty acid methyl ester	[144]
	Starch	[156]
Cellulase	Astragalus polysaccharides	[45]
Glycosidases	Glycosides	[146]
	Oligosaccharides	[57, 58]
Yeast	Trehalose	[78]
	β-lactams	[87]

3.6 Conclusions

From these examples, it is found under microwave irradiation an enhancement in initial rate in comparison with conventional heating method. This led to a reduction in reaction time to obtain a similar conversion. To absorb microwave radiations, polar reactants have more tendencies compared to less polar reactants, which resulted in supermolecular heating. An enhance in temperature can cause molecules to act quickly and head to more number of energetic interactions. With microwave energy, this process happens more quickly due to the high instantaneous heating of the substances over the usual bulk temperature. This might be the elemental thing for the detected rate enhancements. Under microwave irradiation, enzymes may act to some stage in an unusual way and arise to be more efficient. The given examples demonstrated the synergistic effect among enzymatic catalysis and microwave irradiation. Microwaves make various biological actions on enzymes counting upon the strength of the field, waveform, frequencies, duration of exposure, and modulation.

Studies have demonstrated that by microwave heating the activity, selectivity, and stability of the enzyme can be bettered. At the same time, because of the high temperatures affiliated with microwave heating, in enzymatic synthesis, the application of microwave irradiation stays yet bounded as enzymes are very temperature-sensitive molecules. Using new technologies various investigations are going by sustaining accurate power inputs and by keeping the temperature as low as 40 °C.

Although not widely used and popular like chemical synthesis, microwave-induced enzymatic reactions have already been applied successfully in diverse processes. For example, in this review, we have discussed esterification, trans esterification, hydrolysis, transglycosylation, deglycosylation, ring-opening polymerization, optical resolution, oxidation, reduction, and condensation. Undoubtedly, many other enzyme-catalyzed microwave-assisted reactions toward drugs and drug candidates will be discovered in the near future. Based on our expertise, we believe that this is just the beginning of great science.

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Kantharaju Kamanna*

4 Organocatalysts based on natural and modified amino acids for asymmetric reactions

Abstract: Small organic molecules predominantly containing C, H, O, N, S and P element are found promising molecule to accelerate chemical reactions and are named organocatalysis. In addition, these organocatalysts are easy availability, stable in water and air, inexpensive, and low toxicity, which confer a huge direct application in organic synthesis when compared to transition metal catalyzed reactions and becoming powerful tools in the construction of a selective chiral product. Interest on organocatalysis is spectacularly increased since last two decades, due to the novelty of the concept and selectivity. Based on the nature of the organocatalysts used, they are classified in to four major classes, among them one of the types is amino acids derived organocatalysts. Natural amino acids are playing important role in building blocks of protein construction, and also intermediate products of the metabolism. α-Amino acid is a molecule, that contains both amine and carboxyl functional group. Their particular structural characteristic determines their role in protein synthesis, and bifunctional asymmetric catalysts for stereoselective synthesis. Two functional groups present on a single carbon acting as an acid and base, which promote chemical transformations in concert similar to the enzymatic catalysis. The post translational derivatives of natural α-amino acids include 4-hydroxy-L-proline and 4-amino-L-proline scaffolds, and its synthetic variants based organocatalysts, whose catalytic activity is well documented. This chapter discussed past and present development of the organocatalysts derived from natural and modified amino acids for various important organic transformations reviewed.

Keywords: amino acids; asymmetric synthesis; modified; organocatalysts; stereoselective.

4.1 Introduction

Asymmetric organocatalysis is a separate class of catalysis, it employed chiral organic small molecule in a catalytic amount to forward the organic reaction to achieve stereoselective product. The organocatalyzed asymmetric synthesis was gained importance after three eminent scientists shared Nobel Prize in chemistry 2001 *viz*., Knowels, Sharpless and Noyori [1–3]. The conventional catalysts employed for the asymmetric synthesis was transition metals and enzymatic methods and recently organocatalysis

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is entered as a third type catalysts and are complementary to each other (Figure 4.1) [4]. Organocatalysts is an organic molecule containing C, H, O, N, S and P, and it is not involved in its skeleton metals, and in substochiometric quantity accelerates chemical reaction. In addition, these organocatalysts are having unique properties make them to prefer in the organic transformation (Figure 4.2) compared to reaction catalyzed by metals [5]. The area of organocatalysts research is spectacularly raised in the last two decades, due to its unique new concept and additionally, the reaction is facile and achieved controlled product without support of the transition metal catalysts. Based on the nature of the organic molecules, organocatalysts are classified in to four major classes; (i) primary and secondary amines and/or acids derived from biopolymers, (ii) synthetic catalysts derived from biomolecules, (iii) hydrogen bond forming organocatalysts, and (iv) ionic liquid derived [6]. The probable pathway of organocatalysis involved in the chemical transformation is shown in Figure 4.3 [7]. Among biopolymer class of organocatalysts, amino acids and its derived molecules emerged spectacular organocatalysts for selective and facile asymmetric synthesis [8]. Amino acids are playing building blocks in biosynthesis of proteins and also intermediate metabolism product. A molecule that contains both carboxyl and amine functional group attached

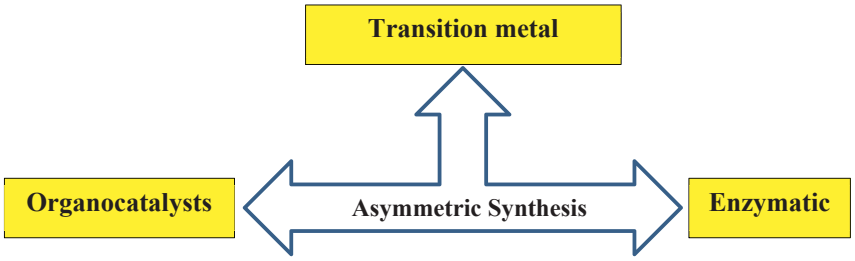


Figure 4.1: Type of catalysts used in organic transformations.

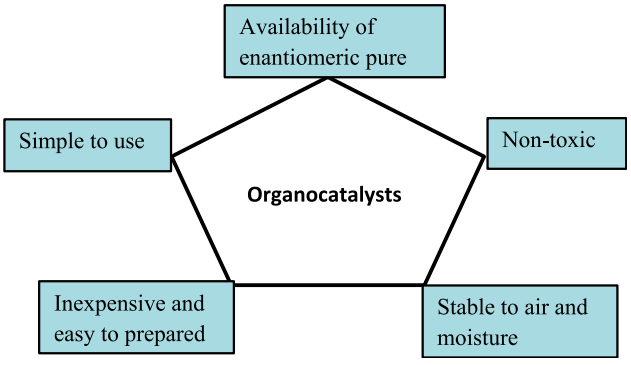


Figure 4.2: Advantage of organocatalysts in organic transformation.

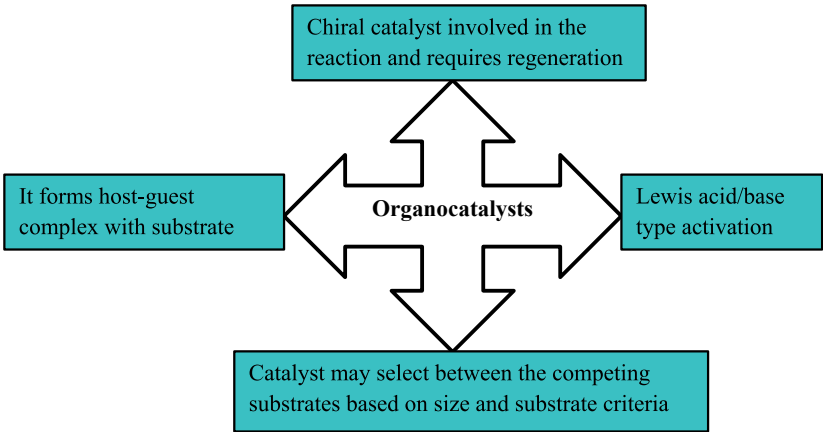


Figure 4.3: Probable four pathways involved in the chemical transformations by organocatalyst.

to the same carbon is called α-amino acid and are commercially available in pure enantiomers. Their unique structural orientation in three dimensional determines their important role in the synthesis of proteins and as a dual functional chiral catalyst for the stereoselective synthesis. Similar to enzyme catalysis, the bifunctional groups can operate as an acid and a base promoting chemical reactions in concert [9]. While all of these criteria apply to main and secondary amine-containing amino acids, the pyrrolidine-based molecules emerged as a superior catalyst [10]. For chemical transformation researchers discovered organocatalytic capabilities of modified amino acids, post-translational derivatives, as well as other synthetic amino acids [11]. Within the domain of asymmetric synthesis, tiny organic molecule able to catalyze an organic reaction is relatively novel concept and admired research topic [12]. Although, the chemical reactions catalyzed organocatalysts have been published in the past century, but in 1998 to till date observed versatile few thousands of research articles published in the area of the organocatalysts in more than 130 different types of the organic reactions [13]. It is now successfully accepted organocatalysts for the enantioselective organic syntheses like other methods used enzymatic and organometallic catalysts. Between 1968 and 1997, there were only a few research articles reported on the use of organocatalysts for the asymmetric synthesis [14]. Late 1990s, Shi, Denmark and Yang with their co-workers reported first time enantiomeric ketone catalyzed simple alkenes to epoxide selectively [15–17]. Later, Corey and Jacobsen group reported asymmetric Strecker reaction using hydrogen bonding catalysts [18, 19] and Miller group demonstrated selective kinetic resolution of alcohols using small peptides [20]. Although, the organocatalysts research in the inception not conceptualize, but it showed path to solve critical hitch of the asymmetric synthesis. In the year 2000, two publications almost simultaneously appeared was effectively launched in the field of organocatalysts from List, Barbas and Lerner on enamine catalysts [21], and another

MacMillan group on iminium catalysts [22]. The paper published by Lerner, Barbas and List highlighted fundamental mechanism of the Hajos–Parrish reaction and extended the transformation to broader application especially for intermolecular aldol reaction. This organic transformation catalyzed by a tiny organic molecule L-proline catalyzes the reaction as larger enzyme molecule does. In this book chapter, we have discussed reported organocatalysts reaction of the natural amino acids, modified proline and a *trans*-Hydroxy proline derivative used in the asymmetric synthesis.

4.1.1 Organocatalysts based on natural and modified amino acids

4.1.1.1 Natural occurring proline amino acid as an organocatalyst

Mother Nature is an utter expert in making various asymmetric reactions and enzymes emerged as high potent biocatalysts in living systems [23]. The catalytic activity of the enzyme found outstanding *via* physical interaction at active sites involved to engage substrates are Vander-Waal forces, hydrogen bonding, hydrophobic, dipole–dipole and electrostatic interactions [24]. Researchers discovered a small organic molecule making in to the above interactions in a chemical transformation [25]. Hence, finding a tiny organic molecule as a catalyst is an alternative to enzyme mimetic represents a very promising and extremely economic [26]. Some of the natural amino acids are extensively studied in their catalytic ability is shown in Figure 4.4. Among them L-proline (**OC-1**) is emerged as a spectacular organocatalyst in the natural amino acid series [27], because it is a rigid ring structure with secondary amine pyrrolidine skeleton played special role in catalysis compared to primary amino acids [28]. To find unique properties of the proline-catalyzed organic reactions, an exhaustive research program is developed on proline-based bioactive compounds, organocatalysts, and ligands [29–31]. Naturally aldolases-I enzyme catalyze aldol reaction through enamine route, similarly researchers discovered same reactions catalyzed by small organic molecule **OC-1** [32]. The surprising matter is that, only **OC-1** and it analogue derivatives have extensively explored in the organocatalysis, while potential of other natural α-amino acids showed relatively lesser catalytic activity and is discussed in the following subsection. The first enantioselective organocatalytic reaction reported in the

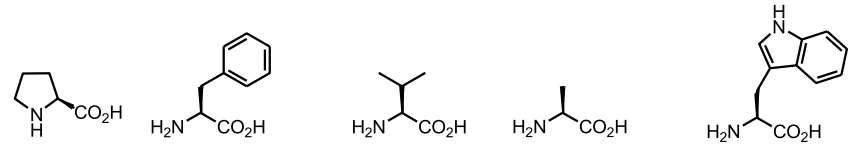


Figure 4.4: Some of the prominent natural amino acid organocatalysts.

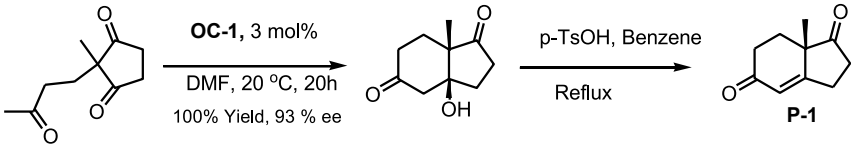


Figure 4.5: Hajos–Parrish–Eder–Sauer–Wiechert reaction catalyzed **OC-1**.

beginning of the twentieth century (**P-1**, Figure 4.5), and observed selective reaction catalyzed by **OC-1** for the optically active steroid partial structure generated by Parrish, Hajos, Sauer, Eder and Wiechert in 1971 [33, 34]. Thereafter, **OC-1** has proven to be a real workhorse molecule in the organocatalysts. The **OC-1** is exploited in variety of carbonyl compound transformations, where the catalysis path involved *via* iminium intermediate. In 2000, the first success of **OC-**1 as a catalyst for the direct intermolecular aldol asymmetric reaction of acetone in excess with *p*-NO_2-benzaldehyde in DMSO (dimethyl sulfoxide) gave desired aldol adduct (**P-2**, Figure 4.6) in 68% yield with 76% enantiomeric excess (*ee*) [35]. The same authors examined other different commercially available amino acids, and emerged **OC-1** and *trans*-4-hydroxy-L-proline as best organocatalysts. Further, Houk's group thoroughly studied the mechanistic route and theory of aldol reaction, and accepted transition state of the **OC-1** catalyzed reaction is outlined in Figure 4.7 [36, 37]. The model reaction provides **OC-1** behaves dual-mode

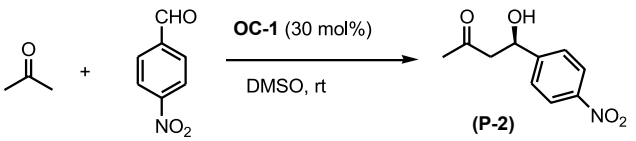


Figure 4.6: Direct aldol reaction.

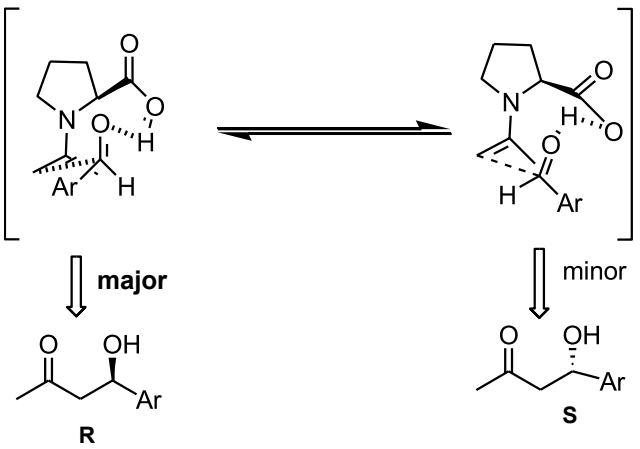


Figure 4.7: Houk's group proposed transition states of the **OC-1** catalyzed aldol reactions.

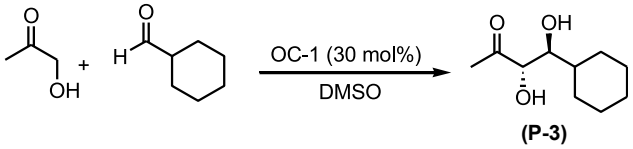


Figure 4.8: Aldol reaction of *anti*-1,2-diol derivative synthesis.

activation leading to *re*-facial selectivity resulted in one type of the product major. In a typical reaction hydroxyacetone as a ketone donor reacts with aldehyde (example cyclohexyl) gave *anti*-1,2-diol derivative (**P-3**, Figure 4.8) up to *ee* >99% [38]. In this case, the reaction proceeds only at the more substituted carbon atom. Other examples employing various ketone-aldehyde combinations clearly revealed generality of the **OC-1** in aldol asymmetric reaction of various substituted derivatives of *γ*-amino-*β*-hydroxyketone with N-protected (Bn = Benzoyl) *α*-amino aldehydes gave excellent yields with *ee* (**P-4**, **P-5** and **P-6**, Figure 4.9) [39].

The aldol asymmetric reaction of formaldehyde and cyclohexanone gave *α*-hydroxymethylation with >99% *ee* [40] and convenient route to construct 3-pentanone *via* thiopyranone gave excellent enantioselectivity [41]. Researcher also demonstrated the presence of aqueous media in a reaction could accelerate aldol reaction improved enantio-selectivity considerably in presence of an organic additive [42]. The synthetic application of the catalyst **OC-1** is extended to other substrates such as 2-hydroxyacetophenone and thiomethoxyacetone for the asymmetric aldol reaction [43]. The major drawback observed in the aldol reaction required high boiling polar solvents (DMSO/DMF), lead relatively reaction time longer, and significant amount of by-products formation [44]. The by-products (enone) formation indicates, the normal Mannich-type and aldol processes competing with each other catalyzed by **OC-1**. The rate of the reaction might be overcome under high pressure reaction condition, and decrease nucleophilicity of the acetone (p*K*a 26.5 in DMSO) [45] compared enamine in a neutral reaction condition. The literature data revealed in major reaction, the direct

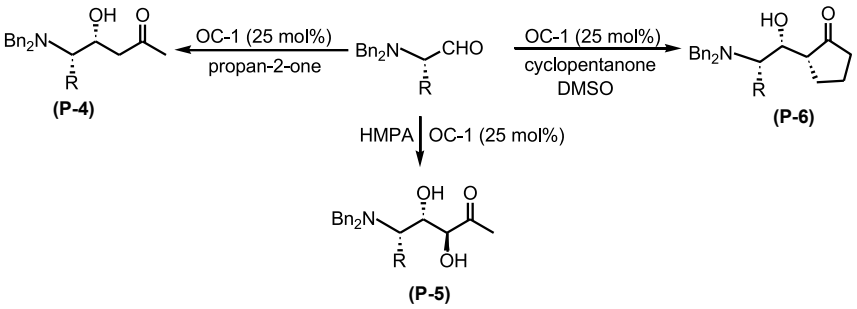


Figure 4.9: Asymmetric aldol product of *anti*-1,2-diol and chiral *α*-amino aldehydes.

combination of ketone and α-unsubstituted aldehyde catalyzed by **OC-1** does not give expected aldol adducts in good yields [46]. Moreover **OC-1** catalyzed aldol asymmetric reactions extended to a various activated carbonyl as aldol acceptors are ketomalonates [47], phenylglycolates [48], acyl cyanides [49], α-keto phosphonates, 1,2-diketones, trifluoroacetaldehyde ethyl hemiacetal [50] and isatins [51]. The solvent plays key role in asymmetric catalysis and discovered various solvent systems for the reaction, and emerged water as a superior eco-friendly universal solvent. Although observed aqueous media had some controversy on organocatalysis [52], but it is found very much useful in the asymmetric reactions due to increasing importance of the eco-friendly benign in recent years. Barbas III and co-workers demonstrated aqueous media for the aldol asymmetric reaction catalyzed by **OC-1** [53]. Thereafter, other research groups demonstrated the reaction rate and selectivity both were enhanced in water compared to other organic solvent used [54], and ionic liquids have also showed significant selectivity [55]. Thus, in many reactions the by-product of Mannich-type product is decreased, and recycled **OC-1** with high yields of the product and *ee* with reaction economy [56]. Various research group considerable effort described **OC-1** catalyzed asymmetric aldol reaction of aldehyde (acceptor) and ketone (donor). In disparity, the effort made recently **OC-1** catalyzed cross-aldol reaction gave direct method to achieve optically active diverse β-hydroxy aldehydes (**P-7**, Figure 4.10) [57]. Further described effective **OC-1** catalyzed cross-aldol asymmetric reaction of amino-acetaldehyde-N-protected as an aldehyde donor, and gave efficient *anti*-β-hydroxy α-amino acids [58]. The utility of a cross-aldol asymmetric product in conjunction with next steps C-C bond formation gave a novel attractive strategy for one-pot construction of polyketide building blocks [59]. The strategy is extended to intramolecular aldol reactions, it provide elegant and expedient method to produce cyclic chiral to acyclic achiral molecules. List et al. reported **OC-1** catalyzed intramolecular aldol reactions of dialdehyde substrates gave high enantioselectivity, and also examined reaction is restricted to only six-membered ring compounds construction [60]. In another work, Pearson et al. demonstrated asymmetric aldol reactions of *meso*-Dialdehydes intra-molecularly to prepare skeleton of tropane alkaloid, and further conversion of aldol product in five-steps gave final (+)-cocaine synthesis in 86% *ee* [61]. In another interesting work researcher reported aldol-related reaction between nitrone act as a nucleophile and presence of reactive carbonyl compound under **OC-1** catalyzed,

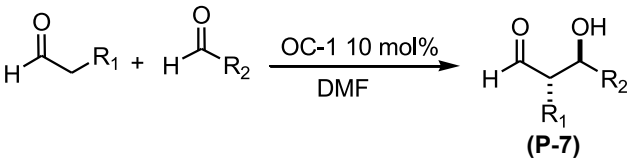


Figure 4.10: Cross-aldol reaction of β-hydroxy aldehyde synthesis.

i.e. nitrone-aldol reaction [62, 63]. The aldol reactions catalyzed by **OC-1** for other methods of C–C bond formation is a versatile strategy for the multi-component self-aldol condensation [64], Knoevenagel [65], Knoevenagel-reduction [66] and aldehyde α-amination [67].

The carbohydrate synthesis catalyzed by enzyme *via* aldol reaction is playing an important role, hence several alternative route to catalyze this biochemical reactions are documented [68]. To succeed this chemistry in the laboratory, various research groups employed proper starting materials carefully. Barbas III et al. employed prebiotic system of three aldehyde substrate assembling in one-pot gave hexose derivatives in the presence of **OC-1** and produce high diastereoseletivity [69]. Later Córdova et al. reported improved *ee* >99% by carefully designing cross-aldol reaction in two-steps catalyzed **OC-1** [70]. This route efficiently produces contiguous four stereogenic carbon centers and very good stereo control. The use of α-oxygenated aldehydes both aldol donor and acceptor give a new route to construct polyol carbohydrates skeleton. MacMillan et al. demonstrated accordingly efficient route for the polyol differentially protected compound synthesis with excellent enantioselectivity [71]. Another more efficient approach reported in this area tandem cross-aldol reaction with Horner–Wadsworth–Emmons olefination gave altronic acid lactone asymmetric synthesis followed by dihydroxylation of olefins diastereoselectively and manipulation of essential entire hydroxy functional group gave required carbohydrate framework [72]. The inherent dihydroxyacetone utility or their equivalents in aldol asymmetric reactions are well reported for rapid carbohydrate synthesis. Enders et al. involved in this area and demonstrated new biomimetic method for the related carbohydrate synthesis [73]. In a very similar type of the work, Barbas III et al. [74] Córdova et al. [75] and other research groups [76] established facile and efficient synthesis of carbohydrates including aza-sugars. The **OC-1** catalyzed asymmetric aldol reaction can also be served to synthesize natural products are well documented [77]. For example Pihko et al. successfully demonstrated cross-aldol reaction of propionaldehyde and isobutyraldehyde resulted (–)-prelactone B in only four steps with high diastereoselectivity with overall yield of 22% [78]. Li [79] and Kotsuki group [80] separately reported the synthesis of (–)-(5*R*,6*S*)-6-acetoxyhexadecanolide an oviposition attractant pheromone of mosquito in good enantioselectivity. In another work, Enders group reported the use of dihydroxyacetone strategy *via* aldol sequence for oxygenated natural products with multi-stereogenic centers synthesis and enantioselectivity [81].

4.1.1.2 Mechanistic pathway of OC-1 catalyzed reactions

Apart from being a more abundant and inexpensive of chiral starting material, **OC-1** offers versatile catalyst in various stereoselecive organic transformations. It contains both carboxylic acid and secondary amine functional group act as a bifunctional catalyst. In amino catalysis **OC-1** can act as an electrophile by readily forming iminium ions or as a nucleophile *via* enamine intermediates. It is revealed that, compared to

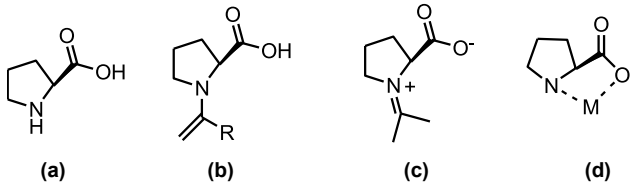


Figure 4.11: Different modes of **OC-1** catalysis; (a) bifunctional acid/base catalysis; (b) enamine catalysis; (c) iminium catalysis and (d) metal-complexes.

other natural amino acids, **OC-1** showed higher pK_a due to its cyclic pyrrolidine structure affecting its hydrogen-bonding strength [82], and its ring allows to form quick enamine and iminium ions more than other cyclic amines (Figure 4.11) [29]. Although **OC-1** catalyzed aldol reaction looks simple, the basic mechanism enroute to other similar addition reactions was the scientific debate and discussion over the last decade. Some of the fundamental issues concern to understanding the intermediate formation, the stereochemistry of the product, influence of carboxylate, and solvent effects. Both theoretical and experimental proof is the crucial components to fully understanding the complexity of this valuable reaction. Nature continues to provide exceptionally well synthetic tool for the facile synthesis of asymmetric molecules under mild condition, aldolase enzymes is merely another example of Nature's reaction to perform asymmetric aldol reactions of highly functionalized carbonyl groups without activation and protection gave highly efficient and chemoselectivities [83]. In light of such enzymatic reactions, the mechanistic pathway of Hajos–Parrish–Eder–Sauer–Wiechert reaction was postulated to occur *via* a similar pathway of class-I aldolase-catalyzed reactions [84]. Key to this school of thought was that, proline-based amino catalysis occurred *via* an enamine intermediate. Hajos and Parrish also alternatively proposed a mechanistic pathway, which employed a carbinolamine intermediate. For the second mechanistic, Hajos and Parrish conjectured that proline formed a nucleophilic enamine intermediate is responsible for the carbon–carbon bond formation that occurs simultaneously with hydrogen transfer. The experimental data supported the

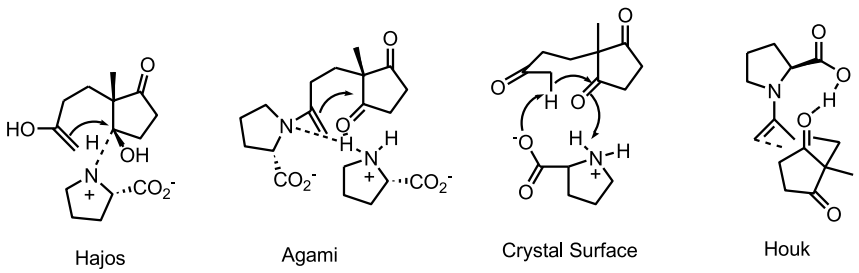


Figure 4.12: Different pathway mechanism of **OC-1** catalyzed reaction reported.

enamine intermediate taking place between substrate and **OC-1** (Figure 4.12) [85–87]. Additionally, stereochemical models disfavored the carbinolamine intermediate as retention of configuration *via* a S_N2-like process would be expected [84]. In another hypothesis, Swaminathan et al. suggested that, **OC-1** acts as a bifunctional catalyst, aldolisation occurs on the heterogeneous surface of the **OC-1** based on its poor solubility in organic solvent [88]. Another issue of contention was whether the **OC-1** catalyzed aldol condensation occurred *via* a one-proline or two-proline model. Agami proposed a two-enamine model, where the first proline molecule engaged in enamine formation and the other proline involved in proton transfer mediator (Figure 4.12) [89]. The experimental intramolecular HPESW reaction showed a nonlinear effect supporting **OC-1** involved two molecules in the enantioselectivity determining step [29]. However by re-addressing Agami's kinetic experiments using HPLC instead of rotations, List et al. demonstrated first order **OC-1** involved, and could not be replicated Agami's concept [84]. Later Houk et al. by density field theory (DFT) calculation described one-enamine route and reported **OC-1** carboxylate group playing major role in proton-transfer step [89]. Further List et al. able to resolved ten different **OC-1** derived enamine crystal structures, which enabled strong evidence to stereochemical control by **OC-1** (Figure 4.12) [90]. Furthermore Engeser et al. [91] and Gschwind et al. [92] studied *in situ* detection of enamine intermediates *via* NMR and ESI mass spectrometry, which also supported an **OC-1** takes enamine pathway. Based on experimental result of **OC-1** forming enamine intermediate, it attacks the aldehydic carbonyl group with high enantiofacial selectivity *via* hydrogen-bond framework.

Researcher also studied for the Mannich-type reactions, a chair-like transition state take place similar to the aldol mechanism proposed, organocatalysts **OC-1** direct nucleophile *si*-facial to (*E*)-imine by the *si*-face of an enamine derived from aldehyde. Unlike aldol reaction, the Mannich reaction found higher enantioselectivity even in the presence of high aqueous media, which is responsible for the lower enantioselectivity in case of aldol reactions [93]. Houk group reported this observation by complete proton migrated to the imine in the transition state through a more substantial ionic force of attraction between iminium and carboxylate as compared to the aldol. Notably compared to the aldol reaction the reverse stereoselectivity is preferred in Mannich reaction. This is explained by the greater stability of the (*E*)-imine compared to the (*Z*)-imine forcing the *R*-substituents into a *pseudo*-axial arrangement (Figure 4.13) [93]. Other type reaction similar to Mannich reaction α-amination and α-oxyamination shared similar ionic interaction leading to the excellent enantiofacial discrimination [94]. An exception is the Michael reaction of nitrostyrene, where the force of attraction between proline carboxylate and electrophile is not optimal (Figure 4.14). Compared to other proline derivatives, electronic interactions lead to attack from above, whereas other sterically encumbered derivatives are employed to promote attack from below [95].

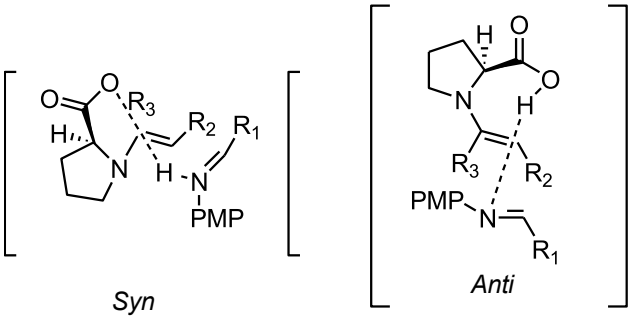


Figure 4.13: Stereochemical model for the *syn*-product favoring in Mannich reaction.

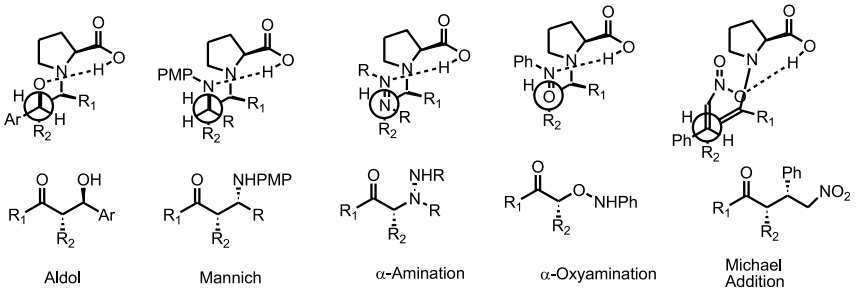


Figure 4.14: Overall comparison of transition states of **OC-1** catalyzed addition reactions.

4.1.1.3 Michael reactions

After successful exploitation of **OC-1** catalyzed asymmetric aldol reactions, only few examples of **OC-1** catalyzed Michael additions are available in the literature, most of the reported reactions gave only moderate selectivity. Wong et al. in his computational work assumed intramolecular hydrogen bonding take place including carboxyl group of the proline and does not involved relevant transition state for the Michael addition. But such hydrogen-bond transition states are found to be important in **OC-1** catalyzed asymmetric aldol reactions [96]. First work related to this conjugated addition of an aldehyde to *trans*-(*β*)-nitrostyrenes (Figure 4.15) [97] reported and observed nitrostyrene is relatively reactive electrophile, and easy to give a Michael-addition reactions. Interestingly **OC-1** provided *syn*-(*R*,*S*)-Michael addition product (**P-8**, Figure 4.15(a)) when aldehyde used as a substrate, and *syn*-(*S*,*R*)-Michael products (**P-9**, Figure 4.15(b)) obtained in the case of ketone. This reversal selectivity underlined the fact that, the reaction is a substrate-dependent and not various mode of action of the catalyst applied. List et al. reported initial data of conjugated addition of ketone to nitrostyrene gave similar results with low enantioselectivity (23% *ee*) [98]. Enders et al. reported improved condition to obtain the desired Michael product in 57% *ee* (**P-9**) [99]. Again,

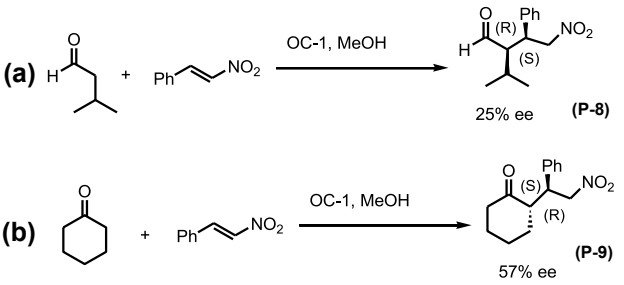


Figure 4.15: Michael addition to *trans*-β-nitrostyrene catalyzed by **OC-1**.

researcher reported reduced reaction time for the product **P-9** using ionic liquids with high *ee* [100].

4.1.1.4 Mannich reactions

Direct Mannich asymmetric reaction is readily accessible to β-amino-ketones or β-amino-aldehydes. Surprisingly **OC-1** emerged as a superior organocatalyst to promote this reaction, and it can be generally divided into Mannich reaction of aldehydes or ketones on one side, and of preformed aldimines or ketimines on the other side. List et al. first time reported three-component Mannich reaction of various aldehydes with *p*-anisidine and excess acetone as a nitrogen source provider gave high selectivity of the *p*-methoxybenzene (PMB)-protected β-amino-ketone (**P-10**, Figure 4.16) [101]. Interestingly the formation of product yield was improved with *ee* by maintaining high pressure of the reactants [102]. Researchers also proved only aldehyde-based **OC-1** catalyzed Mannich reaction is possible and gave *syn*-*y*-amino alcohols after subsequent reduction gave excellent *ee* (**P-11**, Figure 4.17) [103, 104]. The authors also described propionaldehyde slow addition avoids reaction favored cross-aldol or self-Mannich side reactions of the aldehyde. List and co-workers described N-Boc-protected preformed imine reaction with propionaldehyde or acetaldehyde to produce β-amino-aldehydes or alcohols *via* asymmetric Mannich reaction, respectively (**P-12** & **P-13**,

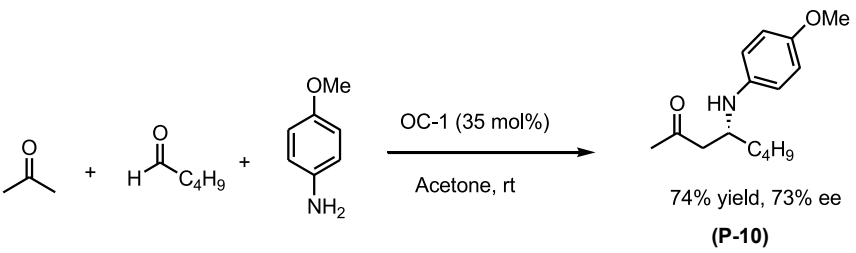


Figure 4.16: **OC-1** catalyzed Mannich reaction.

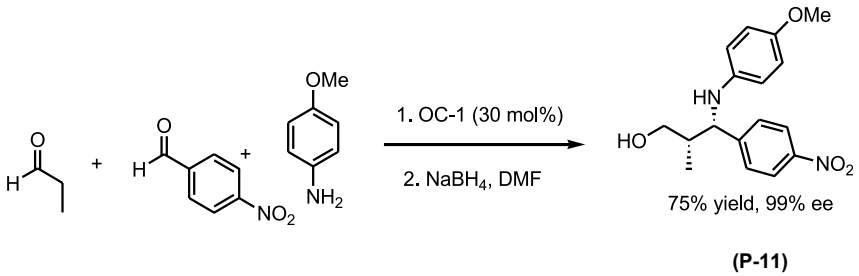


Figure 4.17: **OC-1** catalyzed unmodified aldehydes for asymmetric Mannich reaction.

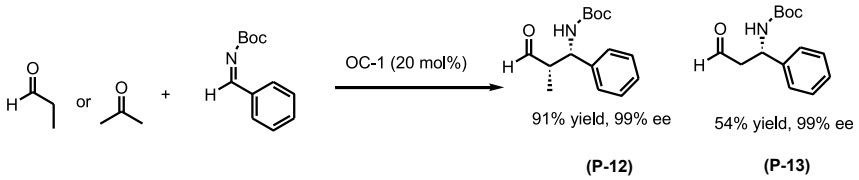


Figure 4.18: Asymmetric Mannich reaction of *N*-Boc-imines preformed with aldehydes.

Figure 4.18) [105]. The advantage of this method is used preformed imines with Boc-protected, after reaction with aldehyde, the product containing Boc-group can be removed under mild condition as compared to other PMP-protecting group used found tedious [106]. Even acetaldehyde is used as an aldehyde source gave β-amino-aldehydes showed extremely useful starting materials in organic synthesis [107]. A similar reaction extended further to a double-Mannich type reaction, since the intermediate formed from a first Mannich reaction itself suitable reactant for the next reaction to produce pseudo-C2-symmetric-β,β'-diaminoaldehydes (**P-14**, Figure 4.19) with high stereoselectivities [108].

4.1.1.5 Miscellaneous and recent reported OC-1 catalyzed reactions

The aza-Morita–Baylis–Hillman (MBH) reaction reported is strategically access enantioselective β-amino carbonyl compounds containing α-alkylidene group, which serve

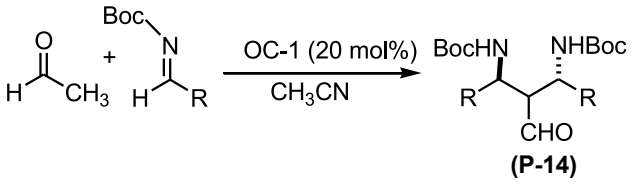


Figure 4.19: Asymmetric Mannich reaction of aldehydes with N-Boc-imines.

as a valuable chiral building blocks are extensively used in the pharmaceutical industries [109]. To achieve this product, authors optimized reaction between crotonaldehyde and a PMP-protected imine gave a high ratio of *E*/*Z* enal excellent yield with *ee* (98%) [109]. *α*-Amination is an addition reaction account for the most direct approach to the formation of chiral molecules with C–N bond formation [110], and azodicarboxylates are exceled better electrophiles for the enamine-mediated addition of ketones or aldehydes. List [111] and Jørgensen et al. [112, 113] described (**P-15**, Figure 4.20) efficient synthesis and widely applicable chiral *α*-hydrazino aldehydes and ketones are found important starting material to generate stable N-amino-oxazolidinones (**P-16**, Figure 4.21) or their respective amino alcohols or amino acids. Bräse et al. later studied added *α*,*α*-disub-stituted aldehydes to the scope of the asymmetric *α*-amination addition thereby forming configurationally stable *α*-amino aldehydes (**P-17**, Figure 4.22) [114].

Furthermore, the *α*-amination reaction combined with acetone gave aldol reaction one-pot product of *β*-amino alcohols (**P-18**, Figure 4.23) in close-to equal amount stereoisomers [67].

Telvekar et al. reported efficient and simple protocol for unsymmetrical N,N′-disubstituted and N-substituted urea derivatives synthesis with excellent yield [115]. In another interesting work, immobilized **OC-1** on magnetic nanoparticles Fe_3O_4-SiO_2-

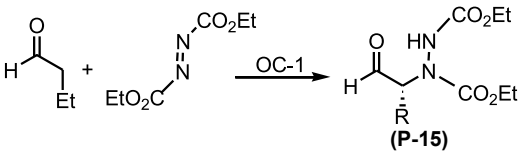


Figure 4.20: Aza-Morita–Baylis–Hillman reaction.

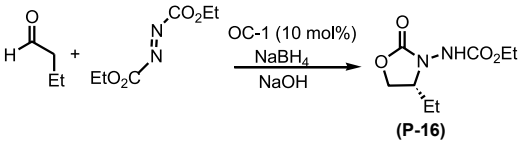


Figure 4.21: Synthesis of N-amino-oxazolidinones.

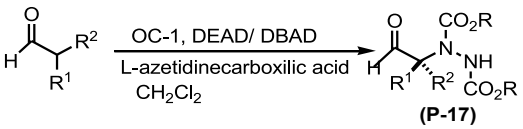


Figure 4.22: Asymmetric *α*-amination of *α*,*α*-disubstituted aldehydes.

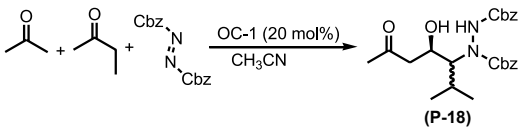


Figure 4.23: Direct asymmetric assembly of optically active *α*-amino alcohols.

propyltriethoxysilane (LPSF) offered easy recoverable of 2,4,6-triarylpyridines in single step solvent-free multi-component reaction of aryl aldehydes, acetophenone, and ammonium acetate produce excellent product yield [116]. Perumal et al. demonstrated efficient one-pot highly substituted functionalized indolylpyrrole derivatives synthesis between *α*-azido ketone, *p*-tolualdehyde and 3-cyanoacetylindole [117]. Qi et al. reported one-pot tetrahydro-4*H*-indol-4-one analogs synthesis *via* cyclohexane-1,3-diones, amines and nitroolefins in the presence of aqueous media catalyzed **OC-1** (10 mol%) [118]. Researcher also studied Hantzsch 1,4-dihydropyridine (DHP) synthesis starting from the aryl aldehyde and cyclic *β*-dicarbonyl dimedone and ammonium acetate in water under reflux condition to achieve hexahydroacridine derivatives [119]. Kumar et al. reported the synthesis of hexahydroquinolines *via* a four-component unsymmetrical Hantzsch condensation of aryl aldehydes, dimedone, acyclic *β*-dicarbonyl compounds and ammonium acetate at ambient temperature [120]. Ji et al. described one-pot preparation of fused pyrazole-1,4-dihydropyridine starting from 5-amino-1-phenyl-3-methylpyrazole, aldehyde and tetronic acid (or 1,3-indanedione) [121]. Many more **OC-1** catalyzed facile and efficient multicomponent reactions are also reported in the review article published by Menéndez group [122]. Behbahani et al. reported four-component synthesis of dihydro-1*H*-indeno [1,2-b]pyridine by combination of aromatic aldehyde, ethyl acetoacetate, ammonium acetate and 1,3-indandione in aqueous reflux condition [123]. A component of naturally abundant antibiotic cyclodepsipeptides of (*S*)- and (*R*)- piperazic acids through asymmetric *α*-hydrazination achieved in 80% yield catalyzed by **OC-1** [124].

Ramachary et al. reported the synthesis of chiral natural products of butenolides, which are showed important biologically active such as (+)-blastmycinone, (−)-blastmycinolactol, (−)-NFX-2, lipidmetabolites, (+)-antimycinone, (+)-homoancepsenolide, mosquito larvicidal butanolide, (+)-ancepsenolide and their derivatives achieved in good yields. In a sequential reaction of *bis*-aldehyde (1,12-dodecanal) and chiral tetronic acid promoted **OC-1** in the presence of palladium-mediated reductive deoxygenation (**P-19**, Figure 4.24) [125] gave a series of enantiospecific butenolides. The same lab described in another work, one-pot Knoevenagel and [4 + 2] cycloaddition of readily available aldehyde, cyclic-1,3-dione and diene in the presence of **OC-1** gave bioactive compounds with an unusual core of spiro[5.5]undecaenes and calliviminones high yield with good regio- and diastereoselectivities [126] (**P-20**, Figure 4.25). In another paper published by the same group described under ambient circumstances a three-component reaction of different propargyl aldehydes, cyclic/acyclic 1,3-diketones and

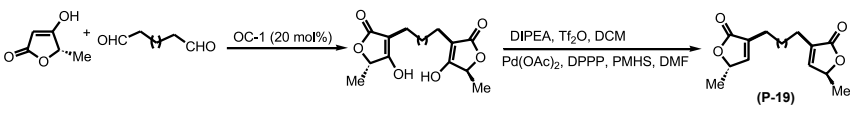


Figure 4.24: Total synthesis of (+)-ancepsenolide.

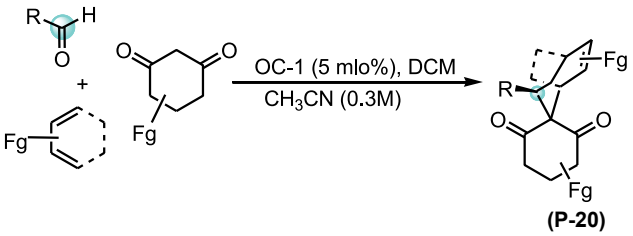


Figure 4.25: Synthesis of calliviminones.

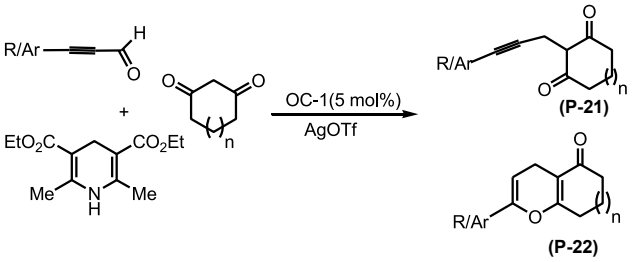


Figure 4.26: Organocatalytic reductive propargylation.

Hantzsch ester catalyzed **OC-1** *via* reductive coupling process gave high-yield of almost fifty propargylated cyclic/acyclic derivatives (**P-21** & **P-22**, Figure 4.26). The authors observed the developed protocol is cost-effective, efficient and metal-free approach produced propargylated cyclic/acyclic compounds on a gram-scale, and many of these molecules isolated in pure state by simple precipitation and not required further use of column chromatography. Authors also explored functionally rich propargylated cyclic-1,3-diketones specifically converted to dihydropyrans (**P-22**), which are generally observed in drugs and natural products *via* annulative etherification catalyzed Lewis-acid (AgOTf) [127]. First time Ramachary and co-workers explained the synergistic catalyst consisting of **OC-1** and simple Bronsted acid TFA (BLA) showed suitable for the List–Lerner–Barbas aldol (LLB-A) reaction of various ketone with less reactive 2-azidobenzaldehyde in room temperature condition. This approach provides first time to access new azido-containing multi-functional molecules in pharmaceutical and material science. Authors reported functionalized chiral 2-azidophenyl alcohols converted into various molecular scaffolds in high selectivity *via* Lewis acid-mediated $NaBH_4$ reduction, azide reduction (Staudinger reaction), and aza-Wittig by oxidative cyclization, click-reaction and allenone synthesis, respectively (**P-23**, Figure 4.27). In medical chemistry chiral LLB-A products could be used as starting materials for many natural products synthesis, ingredients, and inhibitors applications [128]. Further, the same authors demonstrated the synthesis of less-explored biologically important sexually deceptive chiloglottones natural products, antimicrobial dialkyl-resorcinols

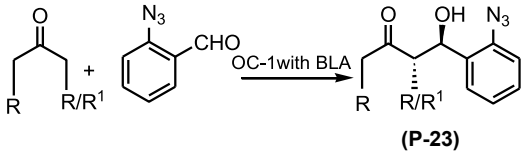


Figure 4.27: Asymmetric LLB-A reaction.

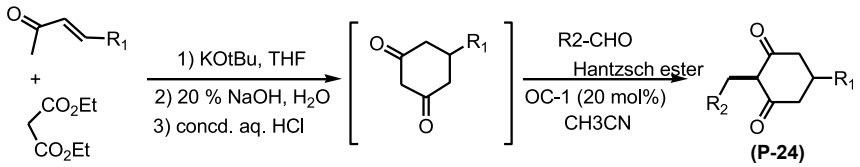


Figure 4.28: Total synthesis of chiloglottone analogue via two-pot/two-step reaction.

various derivatives in a sequential two-pot reaction using "organocatalytic reductive coupling reaction" by functionalized alkylidene-acetone with diethyl malonate under basic and acidic condition afforded 5-alkylcyclohexane-1,3-diones, which were treated with a variety of aldehydes and Hantzsch ester catalyzed by **OC-1** (20 mol-%) at rt gave product **P-24** (Figure 4.28) [129].

Ramachary et al. described three component synthesis of highly functionalized and optically pure spiro [5,5]undecane-1,5,9-triones (**P-25** and **P-26**, Figure 4.29) in a single-step catalyzed by **OC-1**. The method is preferentially accomplished four stereoisomers with >99% *ee*/*de* and excellent yields. Authors also examined *in vivo* screening of these molecules and emerged for the HIV-1 treatment better than the known reference antiretroviral drug azidothymidine (AZT) [130].

Ramachary and co-workers described substituted chiral building blocks synthesis (2-alkyl-CH-acids, 2-alkylcyclohexane-1,3-diones, 2-alkylcyclopentane-1,3-diones, and H-P ketone analogues) *via* multicatalysis cascade (MCC) on three-component reductive alkylation's (TCRA) process. Authors developed alkylation of a variety of CH-acids with (R)-glyceraldehyde acetonide/(S)-Garner aldehyde and Hantzsch ester through **OC-1** catalyzed TCRA reaction without racemization in high yield. The direct sequential TCRA reaction with other cascade reaction like ketenization/alkylation/esterification

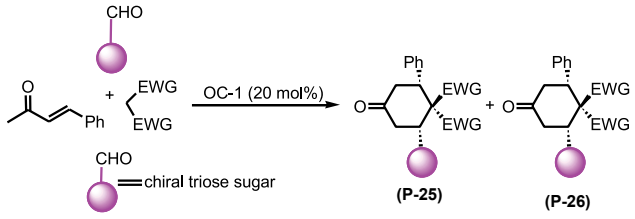


Figure 4.29: General optimization of DTCDA reactions.

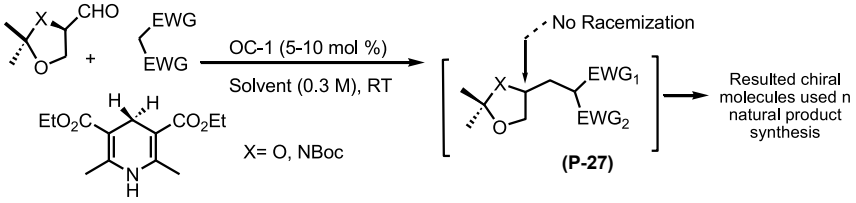


Figure 4.30: Direct amino acid-catalyzed cascade three-component reductive alkylations.

(K/A/E), alkylation/ketenization/esterification/alkylation (A/K/E/A) catalyzed by **OC-1**. The Brønsted acid-catalyzed cascade lactonization/hydrolysis/esterification (L/H/E), hydrolysis/esterification (H/E), hydrolysis/oxy-Michael/dehydration (H/OM/DH), chiral aldehydes, Robinson annulation (RA) of CH-acids, methyl vinyl ketone, Hantzsch ester, various active olefins, and acetylenes produced are chiral building blocks with highly functionalized product in excellent diastereoselectivities and high yields. The authors revealed, major of these molecules are potential chiral building blocks in pharmaceutical and synthesized *via* MCC reactions (**P-27**, Figure 4.30) [131].

Ramachary et al. described the synthesis of tetrahydro-isobenzofuran-1,5-diones having high substituted *via* asymmetric cascade Michael-aldol reaction of alkyl vinyl ketones with 4-hydroxy-3-alkyl-5*H*-furan-2-ones in presence of **OC-1** or 9-amino-9-deoxyepiquinine/TCA. Authors studied the asymmetric synthesis of privileged bicyclic lactones first time *via* kinetic resolution, and showed various applications in natural products and pharmaceuticals synthesis (**P-28** & **P-29**, Figure 4.31) [132]. The same group described novel, metal-free and eco-friendly synthesis of substituted achiral 2-methylchroman-2,4-diols using commercially available 2-hydroxybenzaldehydes, ketones and amines/amino acid catalyzed **OC-1** *via* BLA reactions. Authors examined the fast dynamic equilibrium existence between 2-methylchroman-2,4-diols and 4-hydroxy-4-(2-hydroxyphenyl)-butan-2-one under normal reaction conditions (**P-30** and **P-31**, Figure 4.32) [133].

Ramachary et al. reported copper-free eco-friendly highly substituted α-diazo compounds and NH-1,2,3-triazoles synthesis employing organocatalytic cascade elimination/enamine amination (E/EA) and [3 + 2]-cycloaddition/hydrolysis ([3 + 2]-CA/H) reactions from commercially available azides, activated enones and amino acid/amines. Authors revealed first time an organocatalytic approach based on the push–pull dienamine concept used for the synthesis of *NH*-1,2,3-triazole products (**P-32a** and **P-32b**,

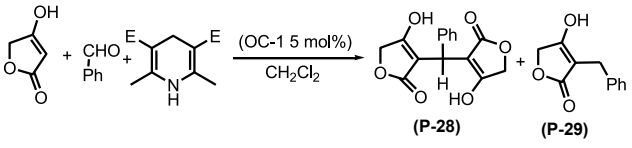


Figure 4.31: Amino acid-catalyzed TCRA reaction with tetronic acid.

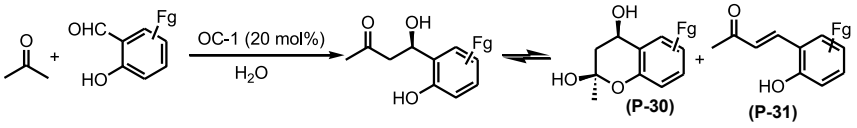


Figure 4.32: Synthesis of achiral aldol-lactol product.

Figure 4.33: Organocatlyzed synthesis of NH-1,2,3-triazole.

Figure 4.33) in good yields [134]. Ramachary and co-workers studied direct amino acid-catalyzed enantioselective and chemo-double cascade process for the synthesis of substituted 2-alkyl-3-methoxy-cyclopent-2-enones, 2-alkyl-cyclopentane-1,3-diones, and Hajos–Parrish (H–P) ketone analogs (**P-33**, Figure 4.34) *via* reductive alkylation. Authors also revealed first time a single-step alkylation of cyclopentane-1,3-dione with ketones/aldehydes a Hantzsch ester *via* an organocatalytic reductive alkylation strategy. A direct combination of **OC-1**-catalyzed hydrogenation-cascade olefination and Robinson annulations of cyclopentane-1,3-dione, ketones/aldehydes, a Hantzsch ester, and methyl vinyl ketone produce H–P ketone functionalized analogues excellent enantioselectivities with high yields. Further, authors examined many more products prepared through reductive alkylation for direct applications in medicinal chemistry [135]. The same group demonstrated a new organocatalytic chemo- and enantioselective cascade preparation of substituted 2-alkyl-cyclohexane-1,3-diones and Wieland–Miescher (W–M) ketone analogs *via* reductive alkylation method. First time authors described one-step alkylation of 1,3-cyclohexanedione and dimedone with aldehydes and Hantzsch ester in presence of an organocatalytic reductive alkylation method. The direct **OC-1**-catalyzed combination of cascade Knoevenagel/hydrogenation and Robinson annulation of CH acids (1,3-cyclohexanedione and dimedone), Hantzsch ester, aldehydes, and methyl vinyl

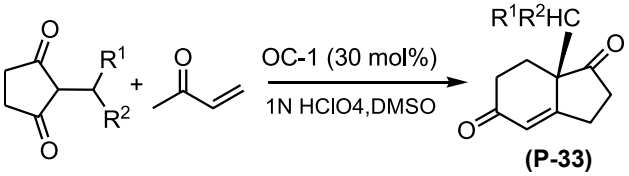


Figure 4.34: Asymmetric synthesis of ketone analogues.

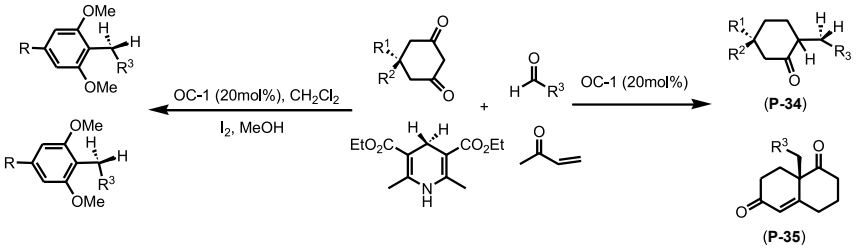


Figure 4.35: Synthesis of 2-alkyl-cyclohexane-1,3-diones and Wieland–Miescher (W–M) ketone analogs.

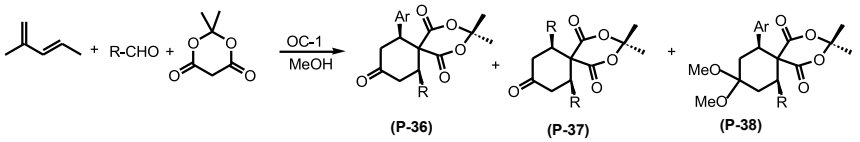


Figure 4.36: Three-component Diels–Alder reactions.

ketone gave W–M ketone functionalized derivatives high yields with excellent *ee*. Further authors showed application of the reductive alkylation products in pharmaceutical chemistry (**P-34** and **P-35**, Figure 4.35) [136]. The same group reported three-component reaction of 4-nitrobenzaldehyde, *trans*-4-phenyl-3-buten-2-one, and Meldrum's acid in methanol catalyzed by **OC-1** gave the Diels–Alder products (**P-36**, **P-37** and **P-38**, Figure 4.36) in high yield with 60% *ee* [137]. **OC-1** Catalyzed asymmetric three-component Diels–Alder (ATCDA) reaction, solvent played significant effect on the rates, yields, and *ee*. Authors revealed the domino Knoevenagel/Diels–Alder reaction catalyzed by **OC-1** produces products **P-36** and **P-37** less yields and good *ee* values in aprotic nonpolar solvents, and excellent yields with moderate to good *ee* in protic solvents [137]. Further, the same research group reported direct **OC-1** catalyzed highly substituted *α*-hydroxy-ketones *via* asymmetric desymmetrization (ADS) of prochiral ketones with optically active. The ADS and O–N bond reduction of prochiral ketone reaction with nitrosobenzene in presence of a **OC-1**-catalytic amount gave tandem ADS/O–N bond reduced products gave high yields and excellent *ee* (**P-39** and **P-40**, Figure 4.37) [138].

4.1.2 Natural primary amino acids catalyzed organic transformations

Although not found exciting results on the natural primary amino acid catalyzed organic transformations, but only few interesting catalyzed reactions so far

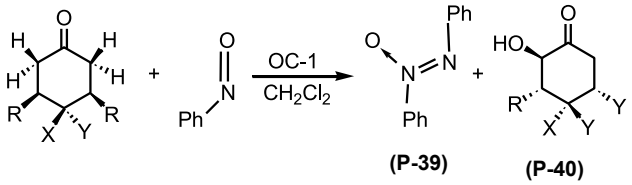


Figure 4.37: Synthesis of optically active α-hydroxy-ketones via asymmetric desymmetrization.

documented in the literature. Eder, Sauer and Wiechert reported **OC-2** can catalyze the intramolecular aldol reactions, but they observed only slightly inferior to **OC-1** [33, 34]. Hajos and Parrish initial work reported, **OC-2** emerged as a surrogate intramolecular aldol reaction catalyst, but enantioselectivity found poor. Danishefsky et al. described slight excess of **OC-2** in the presence of $HClO_4$ gave tremendous optical purity through intramolecular condensation (Figure 4.5) compared to **OC-1** catalyzed reaction [139]. Later different research laboratories are employed **OC-2** with either camphorsulfonic acid or $HClO_4$ to promote key intramolecular aldol reactions for steroid synthesis [140, 141]. Eventhough, less number of organic transformations reported employing primary amino acids, but still in combination with additive reagent or alone demonstrated powerful organocatalysts, which insight way to explore further in a broader scope [142]. The mechanistic route for primary *v*/*s* secondary amino acids through enamine pathway found important activation methods involved in the asymmetric organocatalysis. In this context, limited application is obtained using primary amino acid-promoted enamine catalysis. In fact, the initial study examined by List and Barbas on direct intermolecular asymmetric aldol reactions catalyzed by **OC-1** compared with **OC-2** and **OC-3**, and found later two catalyst (**OC-2** & **OC-3**) gave poor aldol reactions [23, 35]. The catalytic cycle of **OC-1** and primary amino acids *via* enamine formation are well studied and reported [30]. Amedjkouh et al. examined presence of aqueous medium is crucial for aldol reactions to take place in primary amino acid-catalyzed. To summarize all these experimental data suggested primary amino acids are emerged potential catalysts in reactions involving enamine intermediates. In addition, the extra N–H present on enamine intermediate of primary amino group derived control the enamine structure, and direct the reaction more enantioselectivity, but not attainable in proline catalysis. Moreover, the easy commercially optically pure availability of the natural amino acid offers greater diversity and selectivity of the chiral organocatalysts. The most promising work described using **OC-3** as an efficient catalyst in intermolecular aldol reactions of acetone with a variety of aromatic aldehyde gave the product moderate to excellent yields with *ee* (42–72%) [143]. Barbas and Tanaka individually reported organic solvent (e.g. DMSO) with a few drops of aqueous influenced enamine based reactions catalyzed by primary amines [144]. The authors also examined suitable solvent media either DMF or DMSO in a few drops of water gave better results. Further, C´ordova et al. studied series of efficient primary amino acids (**OC-2**, **OC-3**, **OC-4**, and

more) screened for the direct aldol asymmetric reactions of cyclic ketones gave *anti*-selective *β*-hydroxy ketones high yields with 99% *ee* [145–147]. Lu et al. reported the possible hydrophobic primary amino acid-promoted aldol reactions in water resulted optimized hydrophobic interactions, and better transition state defined with high enantioselectivity. For the first time demonstrated tryptophan (**OC-5**), a hydrophobic amino acid is employed for the efficient intermolecular aldol reaction in pure aqueous media as an environmentally-benign reaction of various aryl aldehydes with cyclic ketones gave aldol product high *ee* [148]. Later Amedjkouh described similar aldol reactions in water and organic base as co-catalyst, and observed it facilitates the formation of an enamine and accelerate the reaction [149]. Barbas et al. described facile *anti*-1,2-amino alcohols synthesis using direct Mannich reaction of *p*-anisidine, hydroxyacetone and aromatic aldehyde gave good *anti*-selectivity [150].

4.1.3 OC-1 modified organocatalysts in organic transformations

Since the discovery of **OC-1** tremendously explored as a catalysts, an overwhelming research program on its derivatives has been pursued, namely in the proline-based discovery of bioactive compounds, organocatalysts and ligands. The most developed **OC-1** modified derivatives are used in numerous organic transformations are presented in Figure 4.38. The more elaborated reaction type and product formation catalyzed by proline derivatives for the asymmetric synthesis in selected examples are discussed here. Zhao et al. studied cross-aldol reaction of ketones with *α*-ketophosphonates resulted optically active tertiary *α*-hydroxyphosphonates with high enantioselectivity catalyzed by **OC-6** [151]. The author also demonstrated the compatibility of substituents on *α*-ketophosphonates with alkyl, aryl and alkenyl substituents. The same group reported secondary *α*-hydroxyphosphonates synthesis *via* cross-aldol reaction of ketones and diethyl formylphosphonate hydrate catalyzed by readily available **OC-6** gave high enantioselectivity product (**P-41**, Figure 4.39, up to >99% *ee*) [152].

Wang research group demonstrated a novel method preparation of *α*,*β*-unsaturated aldehyde from alcohol catalyzed **OC-7** and IBX-mediated oxidation [153]. The product obtained high yields and (*E*)-selectivity, these are alkynyl enals and are used in versatile building blocks of polyene and polyyne natural product synthesis. One of its kind dihydroxyerulin is a polyene natural product, which act as a non-cytotoxic inhibitor of cholesterol biosynthesis. The same group reported the preparation of Michael adducts by conjugated addition of novel nucleophilic carbonylmethyl-2-pyridinylsulfone to enals in high enantioselectivity catalyzed **OC-8** (TMS = trimethylsilyl) gave versatile building blocks used in variety of organic reactions [154]. The author screened different hydroxyl protected diphenylprolinol silyl ether, among them **OC-8** (OTES) emerged best catalyst (10 mol%) for enantioselective Michael addition of *β*-methyl ester or *β*-keto pyridine sulfones with *α*, *β*-unsaturated aldehydes [155]. Many research groups reported the use of **OC-8**

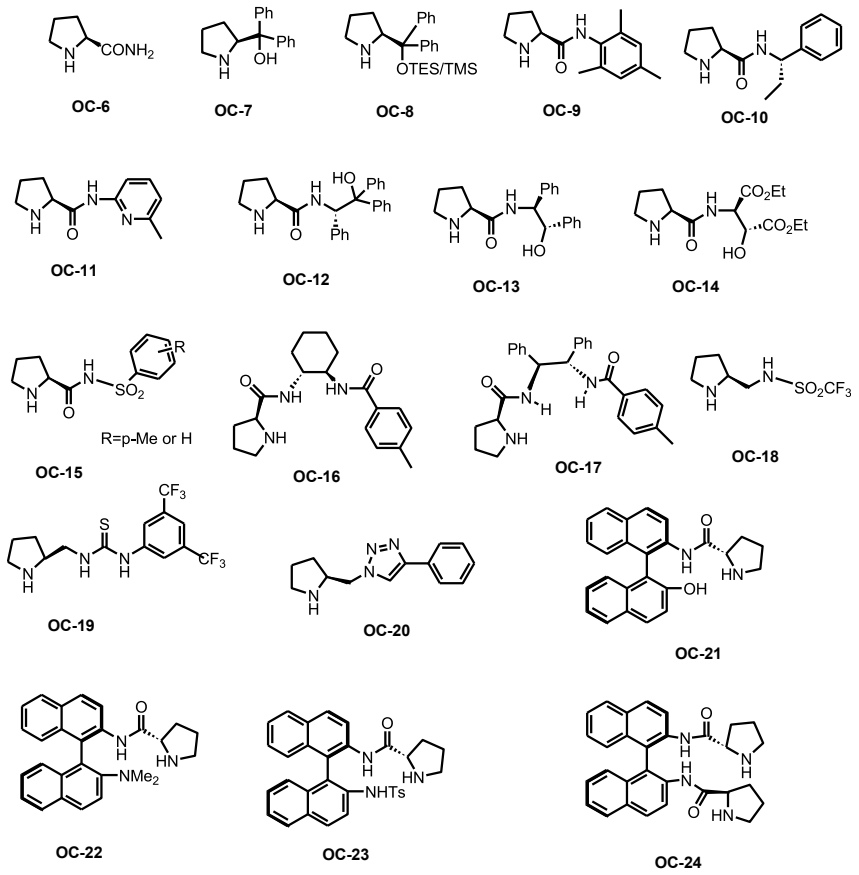


Figure 4.38: Proline modified organocatalysts.

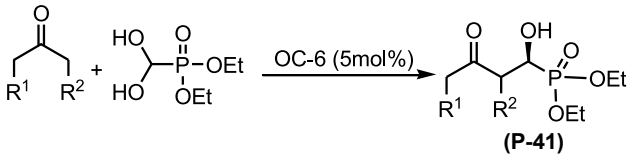


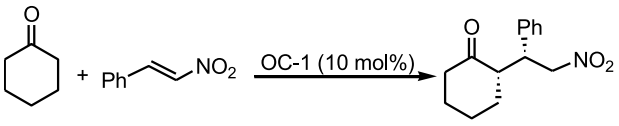
Figure 4.39: Highly enantioselective synthesis of *tert*-R-hydroxyphosphonates.

(OTMS) for the efficient enantioselective synthetic strategy to access 3-substituted-3-hydroxyoxindole *via* conjugated addition of oxindoles and cinnamaldehyde, it is a starting material for many biologically active compounds and natural product synthesis [156]. Researcher reported **OC-8** (OTMS) catalyzed optically pure 2-alkyl-3-(1*H*-indol-3-yl)-4-nitrobutanals synthesis (98% yield, and >99% *ee*) is a one type of tryptamine precursors, which are of great interest in pharmaceutical and biological

research. Gong and co-workers studied elaborately by taking series of L-prolinamide derivatives of L-proline and simple aliphatic 1,2-diphenyl-2-aminoethanols with aromatic amines to direct aldol reaction of chloroacetone and 4-nitrobenzaldehyde [157]. Also they examined the amide proton in the organocatalyst involved in the transition state hydrogen bonding responsible efficient and selective reaction. The catalyst **OC-9** obtained for the reaction of 2,4,6-trimethyl-phenylamine and L-proline emerged as a superior catalyst in direct aldol reaction of aldehydes and chloroacetone in 30 mol% resulted anti-α-chloro-β-hydroxyketones in high *ee*. Chimni et al. reported chiral prolinamide **OC-10** for direct aldol reaction in water solvent gave product good yield and *ee* [153]. Same authors further studied the properties of **OC-10** multifunctional nature and explored joint hydrogen bonding and hydrophobic interactions effect in aqueous media produce chiral β-hydroxyketones in excellent yields (93%) & *ee* (62%) [158]. Gong et al. studied novel various organocatalysts series, which are different position of the substituent on benzene ring for the asymmetric direct aldol reaction of aryl and alkyl α-keto acids with ketones resulted β-hydroxyl carboxylic acids containing tertiary stereogenic center *ee* upto 98%. The catalyst **OC-11** emerged facile reaction of acetone and benzoylformic acid and they demonstrated a single molecule of the catalyst is involved in the catalysis [159]. Sing et al. described novel L-proline-based organocatalysts class (**OC-12**) for the direct aldol reaction between aldehyde and acetone gave good yields of β-hydroxyketones. The authors claimed best product achieved in 5–10 mol % use of catalyst and gave excellent *ee* (97–99%) for both aldehydes of aromatic and aliphatic. Further authors observed for high enantioselectivity *gem*-Diphenyl group presence at β-carbon is necessary and not required chirality at β-position and emerged substituted *i*-Bu and Ph on **OC-12** gave best reaction [160]. Gong and co-workers first time described amides of L-proline amino alcohol (**OC-13**) as a catalysts used for the direct aldol reaction of acetone and aldehyde. The reaction produces up to up to >99% *ee* for aliphatic aldehydes and 93% *ee* aromatic aldehydes [161]. Same authors introduced L-proline amides family derived chiral β-amino alcohols substituted various EDG or EWG at stereogenic centers for direct aldol reaction of acetone and 4-nitrobenzaldehyde. The EWG substituent containing catalyst namely **OC-14** emerged as highest catalytic performance with enantioselectivity than their analogues EDG derived catalyst [162]. Berkessel et al. studied direct aldol asymmetric reaction by novel N-sulfonylcarboxamides (**OC-15**) catalysts, which is known similar acidity as carboxylic acids, and performed direct aldol addition of 4-nitrobenzaldehyde and acetone [163]. Authors reported improved enantioselectivities and reactivity was achieved significantly using various solvents and less loading of catalyst (5–10 mol %) with *ee* (98%), whereas L-proline alone produced maximum *ee* (80%, DMSO). Ley et al. reported **OC-15** catalyzed asymmetric Mannich (cyclohexanone to very reactive N-PMP-protected α-imino ethyl glyoxalate electrophile), nitro-Michael (ketone addition to a nitro-olefin) and Aldol reactions (ketones with *p*-nitrobenzaldehyde) gave products superior to the proline-catalyzed

with respect to *ee* [164]. In another reported work, **OC-15** is employed aldol addition of aromatic aldehyde with acetone in various ionic liquids system gave high yields (98%) with *ee* (50–90%) [165]. Xiao et al. described novel bifunctional and tunable L-prolinamides (**OC-16**) for direct aldol asymmetric reaction of cyclohexanone and aromatic aldehydes derivatives resulted excellent yields (94%) and *ee* (99%) [166]. The same group also studied sterically and electronically tunable bifunctional organocatalyst derivative of **OC-16** to direct aldol reaction of aldehydes and heterocyclic ketones [167]. The catalysts behaved variable effect for analogous substrates, indicating fine-tuning importance to strengthen hydrogen bonding resulted good yield with excellent *ee* of the product (90% to >99%). Xiao et al. prepared novel bifunctional organocatalyst derived from (**OC-17** & **OC-16**) commercially available chiral 1,2-diamines and L-proline to highly efficient direct aldol reactions, indicating the importance of fine-tuning in direct aldol reaction of aldehydes and heterocyclic ketones gave product excellent yield and *ee* (90% to >99%) [166]. Wang and co-workers reported series of reaction catalyzed by pyrrolidine-sulfonamide (**OC-18**) employed in first time to Michael addition of β-nitrostyrenes and α,α-dialkyl aldehydes [168], in this process **OC-18** catalyzes enolization effectively of the α,α-dialkyl aldehyde to achieve electron rich enamine, then add to nitroolefin electrophile. Further authors extended this mechanistic pathway to other electrophilic aldehydes. The aldol reactions of α,α-dialkyl aldehydes as donors with acceptors aldehyde produce β-hydroxyaldehydes excellent yields (up to 97%) and *ee* (up to 97%). Tang and co-workers studied by preparing tunable bifunctional pyrrolidine–thiourea catalyst series (**OC-19**) for Michael asymmetric addition of cyclohexanone to alkyl and aryl nitroolefins in butyric acid (10%) afford high yields of nitro compounds with *ee* (99%) [169]. Liang et al. described catalysts pyrrolidine-based triazole derivatives preparation (**OC-20**), and demonstrated Michael addition of ketone to nitroalkene resulted highly enantioselective product (**P-42**, Figure 4.40) [170].

Lattanzi et al. described (S)-NOBIN-L-prolinamide **OC-21** catalyzed aldol direct reactions of different ketones and aromatic aldehydes in dioxane-water system. Authors observed acetone involved in the reaction gave aldol products *ee* (93%), while cyclic ketones gave low to high yield with *ee* (95%) [171]. Benaglia et al. reported a new multifunctional organocatalysts **OC-22** for the aldol direct condensation of methoxyacetone, acetone or cyclohexanone with various aldehydes gave high enantioselectivity product with high yields [172]. Guillena team described **OC-23** (5 mol%) with



(P-42)

Figure 4.40: Catalytic asymmetric Michael addition of cyclohexanone to nitrostyrene.

additive 1 mol% benzoic acid employed for selective aldol direct reaction of various substituted aldehydes and ketones in solvent-less condition [173]. Author claimed the reaction condition developed required only two equivalent of ketone produce aldol products good yields and *ee*. Further authors also examined **OC-23** capable to catalyze aldol reaction of aldehydes or aldol intramolecular reaction produced excellent yield and *ee*. Najera and team reported aldol direct reaction by BINAM-prolinamide (**OC-24**) catalysts in benzoic acid additive with aqueous DMF gave high yields and enantioselectivities of the product, and recovered catalyst after acid treatment [174]. Author also observed different reactant substrate rate of reaction of acetone and p-nitrobenzaldehyde catalyzed **OC-24** with benzoic acid gave product expected in 86% *ee*. But butan-2-one substrate produces *iso*- and *anti*-isomers in 1:1 isomeric ratio 99% *ee*. In case of cyclohexanone gave anti-aldol 97% *ee*, but cyclopentanone gave opposite diastereoselectivity with lower *ee* (65%) for *syn* & *anti*-isomer (85%). Further, the same group reported the most historically Robinson-type annulation reaction proved most useful strategy for asymmetric Wieland–Miescher ketone (WMK) preparation [175]. It is well-recognized synthon for natural products synthesis established by **OC-24**, one of the BINAM amine is replaced with p-toluenesulfonyl group (2 mol%) catalyzed in presence of additive benzoic acid (0.5 mol%) under solvent-free efficiently produced bicyclic diketones in high yields with excellent enantioselectivities [176].

4.1.4 *trans*-4-Hydroxyproline derived organocatalyst reactions

The functional groups of natural amino acids can undergo modification after post-translational (PTM) inside the biosystem includes acetylation, hydroxylation, *N*-linked glycosylation, methylation and phosphorylation. All these processes represented novel route to expand the family of more derivative of the amino acids. Ever since the more excited results produced by the use of proline based catalysis discovered by Barbas III, List and Lerner, this become a challenging to explore novel and efficient other than proline catalysts. Among them, a new catalyst based *trans*-4-hydroxyproline emerged quite reasonable. Because it contains hydroxyl group lipophilic in nature present on pyrolidine ring can increase solubility, and hence catalytic activity is considerably improved. Typical major reported 4-hydroxyproline derivatives are employed in major organocatlytic reactions are listed in Figure 4.41. It is biosynthesized prolyl-4-hydroxylase [177], a 2-oxoglutarate dioxygenase catalyzes proline-containing peptides & proteins hydroxylation. The presence of an extra hydroxyl group adds an additional source of chirality and provides a functional group that can be used to obtain different derivatives including polymers, fullerenes and ionic organocatalysts. The first report on **OC-25** catalyzed Mannich reaction between alkyl aldehyde and highly electrophilic (*E*)-imine to obtain *syn* α-amino ester (**P-43**, Figure 4.42, PMP = *p*-methoxyphenyl) gave excellent yield with controlled stereochemistry [104]. In another work researcher explored the use of **OC-25** in three-component

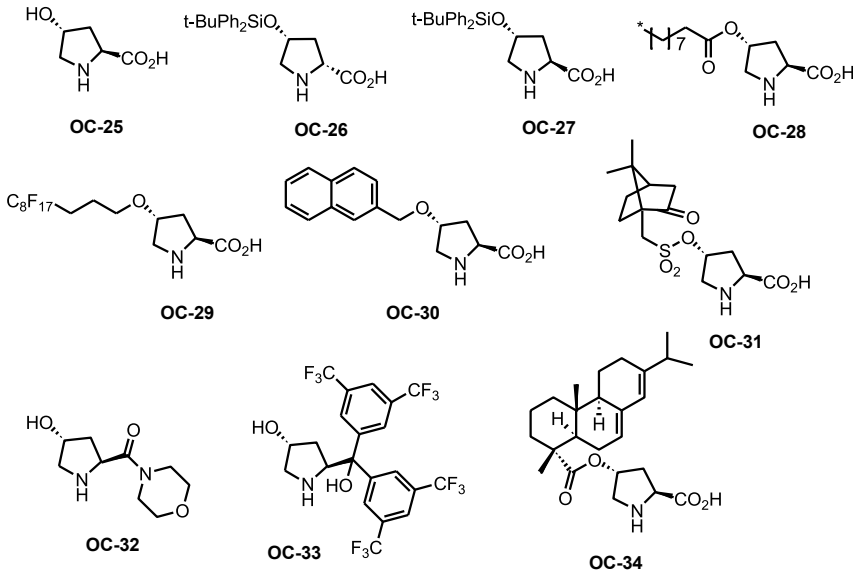


Figure 4.41: *trans*-Hydroxy-proline modified organocatalysts.

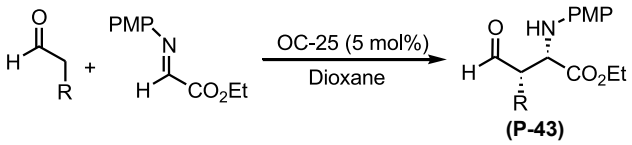


Figure 4.42: One-pot direct asymmetric synthesis of *syn* α-amino ester.

unsymmetric Hantzsch reaction under solvent-free at room temperature condition involving reaction of 1,3-dicarbonyl, aldehydes, and ethylacetoacetate (EAA) gave product polyhydroquinoline derivatives (**P-44**, Figure 4.43) [121]. Iwabuchi et al. reported **OC-26** (*cis*-4-TBDPSroxy-D-proline, 25 mol%) catalyzed synthesis of (–)-CP55,940, a potent inhibitors of cannabinoid receptor achieved by employing novel retroaldolization/aldolization strategy, where temporarily generated aldol

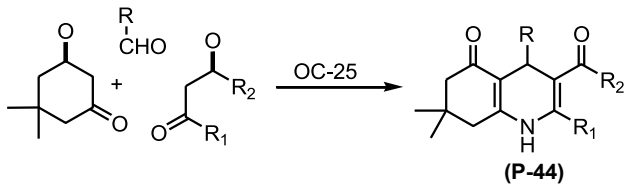


Figure 4.43: Organocatalyzed unsymmetrical Hantzsch reaction.

chiral motif acting as a key building block for the final molecule construction [177177]. The same author reported starting with *σ*-symmetric keto-aldehyde catalyzed by **OC-26** (asymmetric aldolisation) produced *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one greater than 99% *ee* followed by Norrish type-I fragmentation and finally some more step achieved a natural sesquiterpene showed insect juvenile hormone activity (+)-Juvabione with exact structure of the nature abundant [178178]. Hayashi et al. studied the superiority effect of the siloxyproline (**OC-27**) compared to hydroxyproline and proline attributed partially water solubility, and forms an organic phase bridging between ketone and aldehyde in aqueous media gave efficient aldol product with high *ee* (>99%) [179]. In another study, researcher reported direct aldol reaction in aqueous media gave highly enantioselective product [180]. Hayashi and co-workers reported 4-hydroxyproline esters (**OC-28**, $n = 7$) influenced cross-aldol reaction of two different aldehydes in aqueous media, and reaction proceeds smoothly without co-solvent or additive, the long alkyl chain presented on the catalyst gave the final *anti*-aldol products with high *ee* [181]. Further, the idea of amphiphilic and surfactant esters on 4-hydroxy-L-proline (**OC-28**, $n = 9$) examined by Zhong et al. showed extensive substrate scope activity in oil–water interface, and hence, its cross-aldol reaction activity of cyclohexanone and different aryl aldehydes [182]. A polyfluorinated proline derivative (**OC-29**) have fluorine 54% content prepared, and examined for aldol reaction acetone and p-nitrobenzaldehyde gave 73% *ee* [183]. A novel (4R)-4-(*β*-naphthalenyl) methoxy-(S)-proline (**OC-30**) prepared from naturally occurring (4S)-hydroxy-(S)-proline, and catalytic activity for the aldol asymmetric reaction of various benzaldehydes with excess acetone gave aldol adducts high yields and *ee* (89.8%) [184]. In another work, researcher reported (2S,4R)-4-camphorsulfonyloxy-proline (**OC-31**) is employed for aldol reaction and obtained product much higher *ee* compared to proline itself [185]. Amide derivatives of *trans*-4-hydroxy-L-proline (**OC-32**) employed aza-Michael/Henry domino reactions with protected *N*-(2-formylphenyl) sulfonamides and *trans*-*β*-nitroolefins gave chromenes **(P-45**, Figure 4.44) with moderate *ee* (52–88%) [186]. Authors also examined possible mechanism involved transition state depending on protecting group NH. Among different protecting groups tested, tosyl (R_1 = 4-Me-Ph) group emerged best protecting performance for stereoselectivity and reactivity. Xu et al. reported first iminium catalysis of salicylaldehydes and *trans*-*β*-nitro olefins (oxa-Michael–Henry reactions) afforded chiral 3-nitro-2*H*-chromenes using a bifunctional *trans*-4-hydroxy-L-prolinamide as the catalyst and 4-nitrophenol as co-catalyst

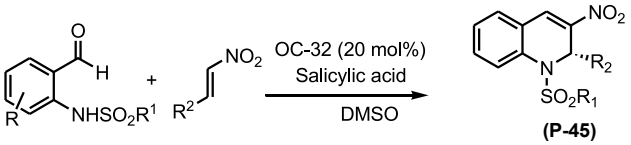


Figure 4.44: Domino aza-Michael–Henry reactions.

[187]. Further Yin et al. improved Xu's method for chiral 3-nitro-2*H*-chromenes synthesis in terms of both yield (99%) & *ee* (90%) under mild reaction condition catalyzed by **OC-32**. Moreover it was found that, the heteroaromatic aldehyde 2-formylpyrrole could also be activated by a transient iminium species [188]. Hayashi et al. reported aldol asymmetric reaction of acetaldehyde and isatin derivatives catalyzed **OC-33** affording aldol product with high enantioselectivity and subsequent reduction achieved 3-hydroxyindole alkaloids [189]. Bhowmick and co-workers described novel catalyst (**OC-34**), which is bearing additional chiral centers provided by abietic acid skeleton and promotes aldol direct reactions of substituted aryl aldehydes with ketones in methanesulfonic acid additive in water gave aldol products in high yields (99%) with *ee* (99.9%) [190]. The authors claimed loading of catalyst drastically reduced to only 1 mol %, and the rate of the reaction extremely faster compared to other organocatalyzed reactions.

4.2 Conclusions

A tremendous quantum of research takes place to naturally occurring compounds as chiral catalysts and chirality generating materials. Amino acids, among the most important molecule in the cycle of terrestrial life, now become emerged in asymmetric synthesis catalysts. The research on asymmetric catalysis using amino acids available in commercially, and especially L-proline and its derivatives pioneering work reported in 2000 by Barbas III, List, and Lerner. As described in this chapter and the previous reviews and publications highlighted by eminent research groups across the globe revealed proline and its modified molecules as an organic catalysts exhibited several benefits, like availability of pure stereoisomers, facile in handling, resistance to air and moisture, and green protocol processes. This might be the main reason for amino acids and its derivatives produced large number of research papers on organocatalysts research. Naturally enzyme catalysis involved in asymmetric aldol reactions showed greater generality and it need development of its mimic proline have reached now practical synthetic catalysis. Moreover, the substantial impact is given to new generic activation modes; it is probable that, various research group is focused their research work focused on this ideal research. Perhaps most important research area on organocatalysis in future identification of more promising reactions, those are not available or impossible by other catalysis method. Given high success and growth of the organocatalysis research in the past, this will certainly focused more exciting research. In the near future, we can expect much more robust organocatalysts discovered, and explored commercial organic transformations.

The more surprise and recognition come true on this organocatalysts field by awarding highest honors to scientists, who really contributed substantial amount of work to this filed. List and MacMillan awarded highest honor of Nobel Prize in Chemistry 2021, for their outstanding contribution towards the development of a smart

novel tool for molecular construction: organocatalysis. This area of research plying important role in pharmaceutical and fine-chemical research, and made protocol greener.

Abbreviations

Boc	*tert*-Butyloxycarbonyl
BINOL	1,1′-Bi(2-naphthol)
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
DHP	1,4-Dihydropyridine
EtOAc	Ethyl Acetate
ee	Enantiomeric excess
EDG	Electron donating group
EWG	Electron withdrawing group
$HClO_4$	Perchloric acid
HOMO	Highest occupied molecular orbital
IPP	Isopentenyl pyrophosphate
i-Bu	iso-Butyl
i-Pr	Iso-propyl
$NaBH_4$	Sodium borohydride
OTMS	O-Trimethoxysilane
Ph	Phenyl
PMP	*p*-Methoxyphenyl
p-tol	*para*-Tolyl
PMB	*p*-Methoxybenzene
t-Bu	*tert*-Butyl
TBABr	Tetrabutylammonium Bromide.

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5 Critical trends in synthetic organic chemistry in terms of organocatalysis

Abstract: The utilization of small organic compounds as catalysts has advanced rapidly, and organocatalysis has emerged as a dominant technique complementary to metal-catalyzed organic conversions. The organocatalysis field has enhanced the progression of innovative approaches to make varied chiral molecules. Researchers have placed enormous effort towards designing and blending simpler organocatalysts to synthesize enantioselective molecules in good yields. This work emphasized the impact of enamine, iminium, hydrogen bonding, and phase transfer organocatalysts in organic synthesis. The monograph focused on the crucial methods to construct valuable molecules with high enantiomeric purity.

Keywords: enamine; hydrogen bonding; iminium; organocatalysis; phase transfer.

5.1 Introduction

The generation of enantiomeric pure organic molecules having chiral centers is a significant achievement in organic synthesis because of their standing in chemical research in the pharmaceutical industry [1]. The design of stereospecific or stereoselective chemical reactions is a challenging area in organic synthesis. In recent days, asymmetric organocatalysts have become a fascinating area for the synthesis of chiral organic molecules. Small organic compounds with highly selective and specific catalytic properties play a significant role in building complex and enantiopure molecular frames [2].

In synthesizing the enantioselective chiral molecules, organic molecules as catalysts is a popular choice. The value of chemical conversions using organocatalysts has been recognized over the past century [3]. The area of organocatalysis has a substantial effect on chemical science. It has established a viable synthetic paradigm and

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has perceived many accomplishments in continually addressing synthetic challenges [4, 5]. The enormous progress in organocatalysis yields a variety of prospective applications in large-scale industrial processes [6]. Therefore, target-oriented developments in organocatalysis are a way forward to incredibly effective, selective, and widely applicable synthetic methodologies in asymmetric synthesis .

In 1832, Wohler and Liebig reported the benzoin reaction by employing an organocatalyst, cyanide, for the first time to create α-hydroxyl ketone [7]. Later in 1860, Liebig used acetaldehyde as an organocatalyst for synthesizing oxamides from cyanogen and water [8]. After some intermittent progress, Bredig and Fiske [9] explored organocatalytic reactions again in 1912, using cinchona alkaloid as an organocatalyst for converting HCN to benzaldehyde with 10% enantioselectivity . In 1960, Pracejus et al. [10] reported an organocatalyst chiral cinchona alkaloid for the metanalysis from ketene with 74% enantioselectivity . In the early seventies, significant recognition occurred to organocatalysis research, achieving high enantioselectivity using L-proline as a catalyst for aldol condensation [11, 12].

A range of small organic molecules has been used as organocatalysts in several chemical reactions [13]. Numerous comprehensive publications are obtainable that provide a complete account of the organocatalysis vicinity and have recently advanced significantly. More than 7112 articles have been published in the specific field (Figure 5.1) [14]. This monograph discussed four modes of organocatalysis (enamine, iminium, H-bonding, and phase transfer), important in synthesizing medicinally beneficial molecules.

5.2 Organocatalysis and mode of activation

Organocatalysis describes a way of catalysis whereby the chemical reaction rate is enhanced by a small organic catalyst mostly involving H, C, N, P, and S elements in

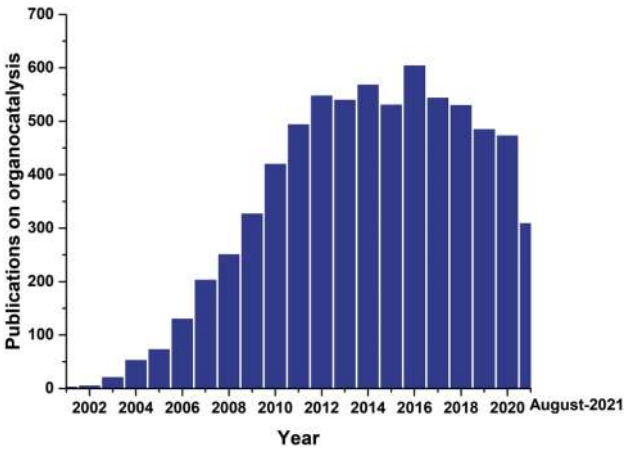


Figure 5.1: Publications on organocatalysis between 2001 to August 2021 (Source Scopus) [14].

organic synthesis. The lack of metal atoms in organocatalyst creates numerous rewards contemplating both green chemistry and economic viewpoint. It is a new organic synthesis approach and mainly an alternate to the ubiquitous transition metal catalysis. The discovery of reactivity and catalyst activation types is an accomplishment in asymmetric organocatalysis over the decade. Based on the mechanism of the catalysis, organocatalysts can be Lewis acids, Brønsted acids, Lewis bases, and Brønsted bases. The catalytic cycle is described in Figure 5.2 [15].

Various organocatalysts have been established depending on affinity capacity by the starting materials interactions via covalent- or noncovalent-bond (H-bonding and ion pair) (Figure 5.3). For example, achiral substrate forms a covalent bond with chiral

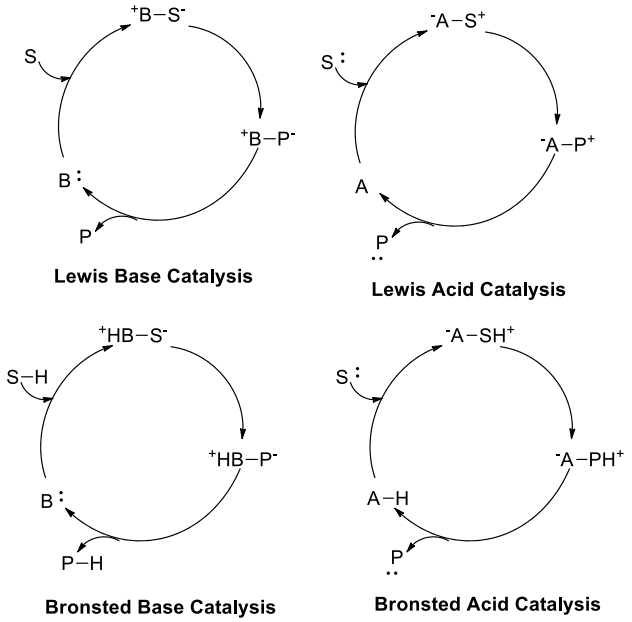


Figure 5.2: Organocatalysis of catalytic cycle.

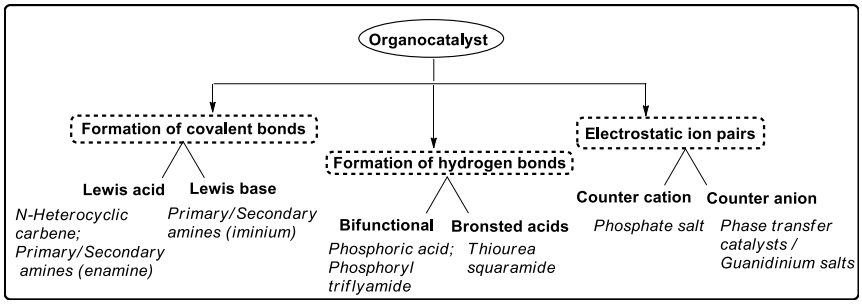


Figure 5.3: General classification of organocatalysts as per activation mode.

organocatalyst, and the transition state involves enamine and iminium activation (Table 5.1). Proline, cinchona alkaloid-amines, and proline-derived amines are involved in such kind of catalytic activation (Figure 5.4) [16–18]. Brønsted acid catalysts (thiourea, phosphory-triflylamides, squaramide, and phosphoric acids) form H-bond with the achiral substrate through a chiral transition state [19–21]. Some chiral organocatalysts (bifunctional catalysts) involved electrostatic interfaces with the achiral substrate [22, 23]. These reactive species connect the chiral catalyst with a fundamental substrate (aldehyde, ketone, imine, and alkene) in a well-arranged manner. The advances in organocatalysts catalyzed chemical reactions are valuable for a broad array of asymmetric chemical reactions.

5.2.1 Enamine catalysis

Enamine catalysis involves an amine-containing bifunctional catalyst. The catalyst interacts with a carbonyl group-containing substrate (ketone and aldehyde) to produce an enamine intermediate. Further, it involves an electrophilic reaction partner. This method of activation is functional in many enantioselective reactions. In 1971, a highly enantioselective product was reported through a proline catalyzed intramolecular aldol reaction [28, 29] (Figure 5.5). Later List et al. have developed enamine catalysis to give the carbonyl-based derivatives at the α-carbon [26, 30].

The *s*-proline catalyst participating mechanism through nucleophilic additions and *α*-deprotonation are viable (Figure 5.6). Deprotonation leads to the production of the enamine, which is further reacted with an aldehyde. Further proceeded through a transition state (TS) and hydrolysis, then offers enantiomerically enriched aldol derivative [31–33].

In recent times, the catalytic production of asymmetric enolate counterparts immensely contributed to the growth of organocatalysis. There have been several subsequent reports of catalytic reactions *via* enamines have been established. List et al. [30] reported an intermolecular procedure involving secondary amine catalysis via enamines to give the highly enantioselective products (Figure 5.7a). The tightly linked Mannich reaction can also be catalyzed by proline to produce *syn*-amino carbonyl compounds that could be transferred to an array of alcohol and amino acid products (Figure 5.7b) [34, 35]. Further, the Mannich reaction is possible through a one-pot imine formation with enantiomeric excess [36]. A remarkable extension of this procedure was described by [37] Northrup and coworkers, which explained the cross-aldehyde aldol coupling (Figure 5.7c) [37, 38]. A necessity of this chemical reaction is that the carbonyl group of aldehydes could be specified as donor or acceptor. This clearly shows one aldehyde can develop an enamine (donor), and the other can behave as the acceptor.

In addition, C–C and C–heteroatom bond development has been investigated with proline catalyst, and various reports are available in the literature [39, 40]. These reactions include the *α*-oxygenation of aldehydes with nitroso benzene. A wide variety

Table 5.1: Most commonly used modes of activation in organocatalysis.

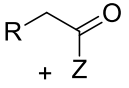
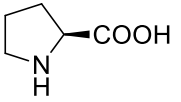
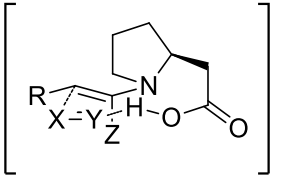
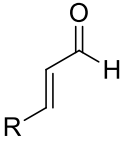
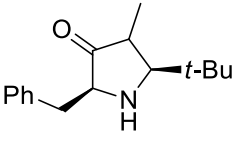
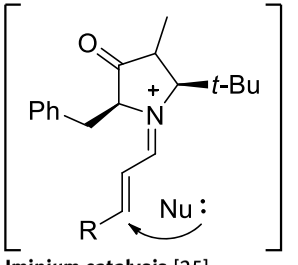
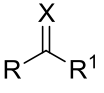
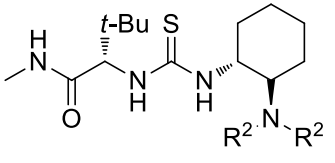
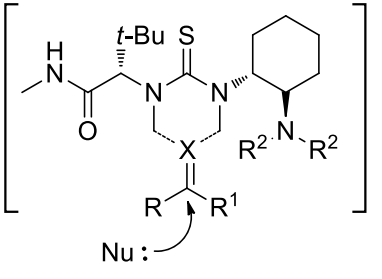
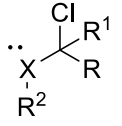
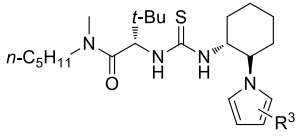
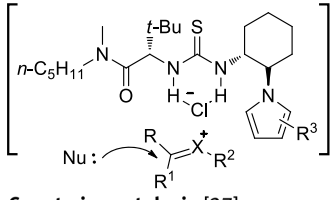
Substrate	Catalyst	Activation mode [Ref]
 X=Y R = Ring system X, Y = C,N,O,S Z = alkyl, H		 **Enamine catalysis** [24]
 R = alkyl, aryl		 **Iminium catalysis** [25]
 X = O, NR R,R^1, R^2 = alkyl, aryl		

Table 5.1: (continued)

Substrate	Catalyst	Activation mode [Ref]
 X = O, NR R,R^1,R^2, R^3 = alkyl, aryl		**Hydrogen-bonding catalysis** [26]  **Counterion catalysis** [27]

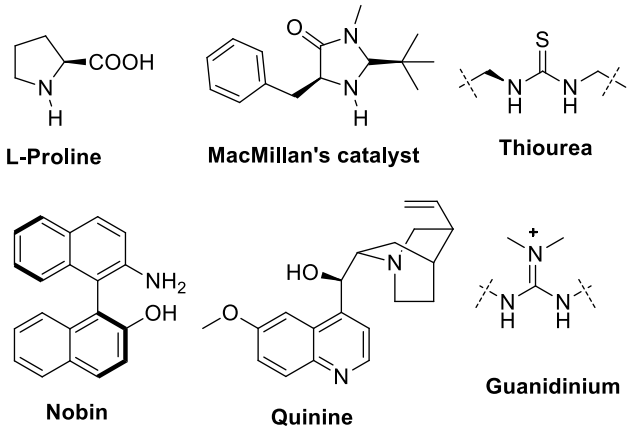


Figure 5.4: Few examples of organocatalysts.

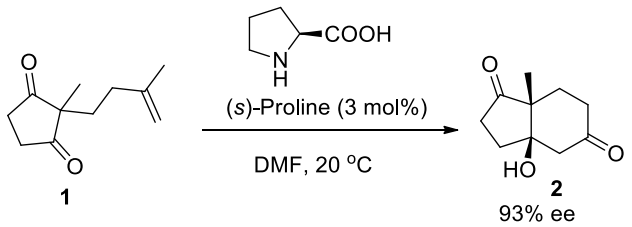


Figure 5.5: Proline catalyzed reaction through enamine activation mode.

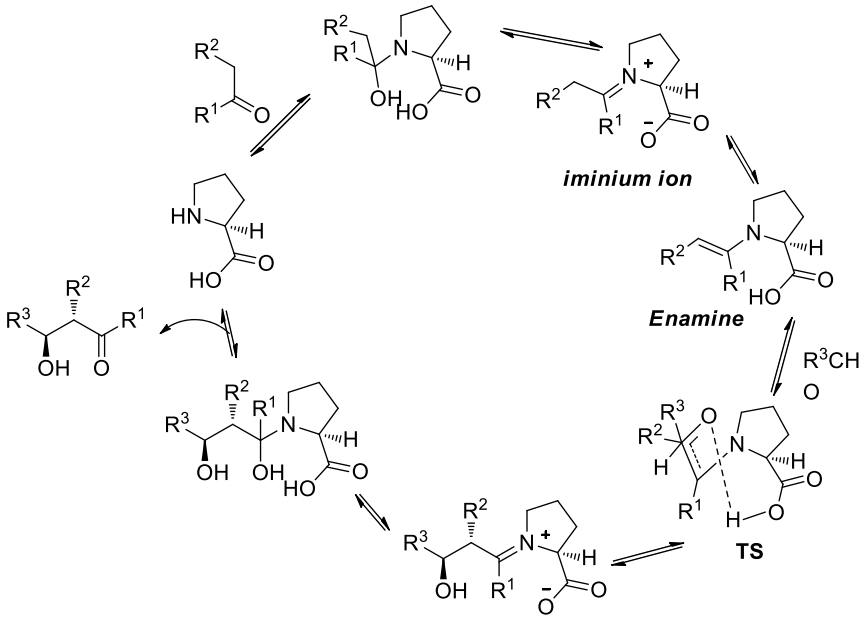


Figure 5.6: The proposed mechanism of proline-catalyzed aldol reaction.

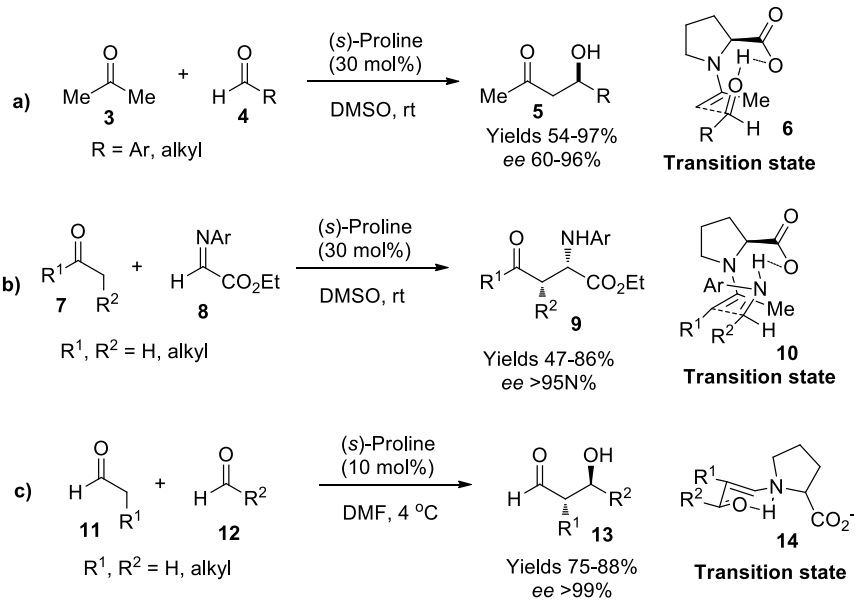


Figure 5.7: Proline-catalyzed reaction through enamine activation mode.

of carbonyls performed well. This easy oxygenation of aldehydes/ketones gives an appropriate method for the swift synthesis of valuable chiral building blocks for organic synthesis (Figure 5.8a) [41]. Additional electrophiles can be applied to intercept enamines. The reaction of enamines with alkyl diazo-dicarboxylates facilitate the production of a nitrogen group in the α-position to the carbonyl group. These can be altered easily into amino acid molecules (Figure 5.8b) [42, 43]. The generation of sulfur-containing moieties with significant enantiomeric excess is beneficial to create effective thiol-based derivatives [44]. The highly essential α-oxidation reaction includes α-chlorination of aldehyde substrates (Figure 5.8c) [45]. The results developed from this reaction are flexible intermediates that may be transformed into an array of various functional molecules (amino acids, aziridines, and epoxides).

The earlier articles on the addition of carbonyl groups to nitro olefins *via* enamines provided merely moderate enantiomeric excesses by proline or proline-derived catalysts [46–48]. A superb example of this reaction is using a prolinol-derived catalyst that gives excellent yields and enantiomeric excesses for this conversion (Figure 5.9a) [49]. Remarkably, the stereochemical control in this reaction appears to be controlled by the steric nature of the catalyst. The addition of enamines to enones is an unruly reaction. Chi et al. have recently demonstrated that pyrrolidine catalyst instantly influences the addition of aldehydes to simple enones in great enantiomeric excess, providing a solution to the drawback (Figure 5.9b) [50, 51]. In addition, silyl glyoxylates and aldehyde involved an aldol reaction with a 4-hydroxyproline organocatalyst described.

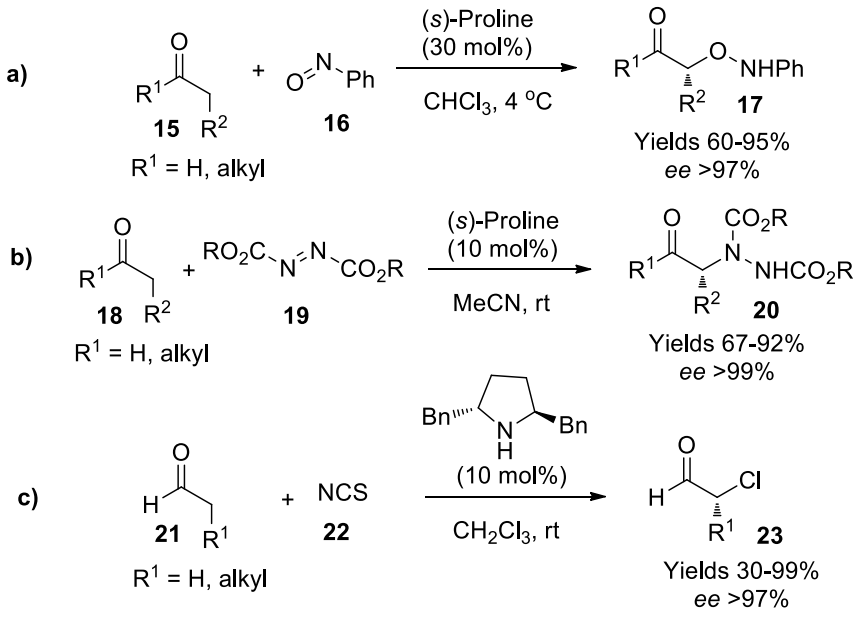


Figure 5.8: Proline catalyzed reaction through enamine activation mode.

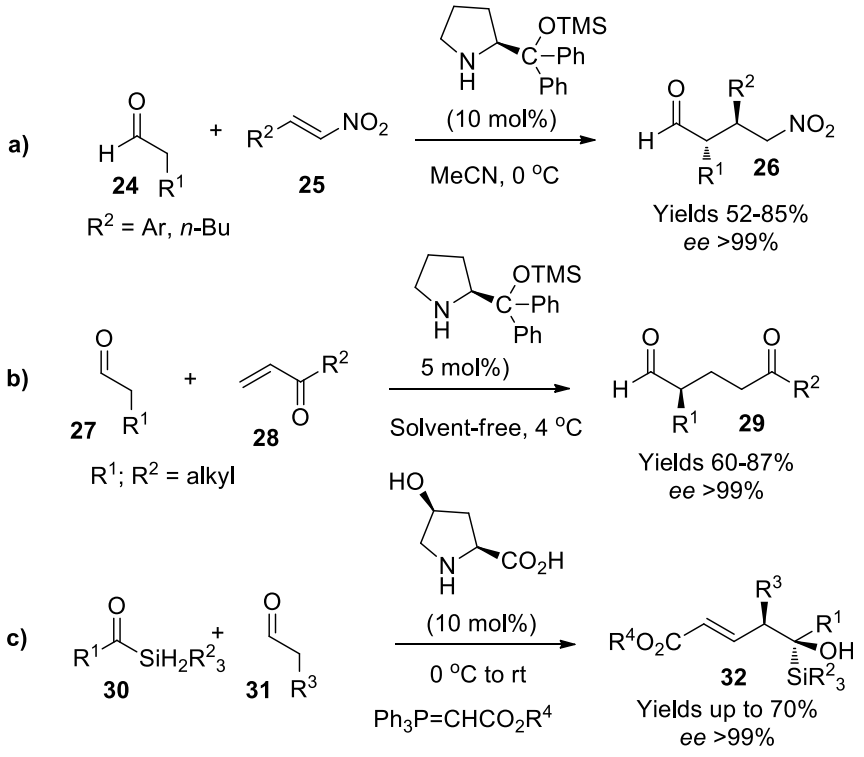


Figure 5.9: Proline-derived catalyst catalyzed reaction through enamine activation mode.

This catalyst is ideal for activating acyl silanes and aldehydes, effectively generates *α*-hydroxy silanes with high enantioselectivities (up to 99% *ee*). A carbonyl group quickly connected to silicon in acyl silanes can be initiated by coordination to the proton of hydroxyl and carboxylic acid *via* a hydrogen bond [52] (Figure 5.9c).

5.2.2 Iminium catalysis

Iminium catalyst is a chiral amine that drives various enantioselective organic conversions, usually needing Lewis acid catalysts [53]. The organocatalysts of chiral secondary amines are used to activate enals *via* the iminium ion. Iminium ion catalysis gives an organocatalytic alternate to traditional Lewis acid catalysis of *α*,*β*-unsaturated derivatives. The iminium species possess a lowered energy LUMO orbital, which can easily interact with suitable partners through a conjugate addition [24, 30]. The transition state of catalyst potential steadiness by a π-interface with the benzyl moiety of the phenylalanine imposes this conformation, and dimethyl moieties influence the iminium ion away from these larger moieties and lead to high selectivity through strike on the alkene (Figure 5.10).

Furthermore, the conjugate addition molecules can sometimes be seized at the enamine step, undertaking multiple bonds emerging processes *via* tandem reactions. The variety of cycloadditions that can be achieved *via* iminium catalysis encompasses conventional [4 + 2], nitrone [3 + 2], and [4 + 3] reactions [54–56]. Typically, these reactions endure a series of diene and dienophile parts and offer broad scope for these catalytic cycloadditions and generate stereoselectivities in good yields and great enantiomeric excesses. Ahrendt has described that enals efficiently endure [4 + 2] cycloadditions with various functionalized dienes with great endo control (Figure 5.11a) [24]. At the same time, the enones are ideal starting materials in the presence of an additional reactive catalyst. It offers a good explanation of the problem of enone cycloadditions of catalytic enantioselective (Figure 5.11b) [54].

Activation *via* iminium ion formation also makes facile conjugate addition methods with soft nucleophiles. A series of aromatic and heteroaromatic nucleophiles

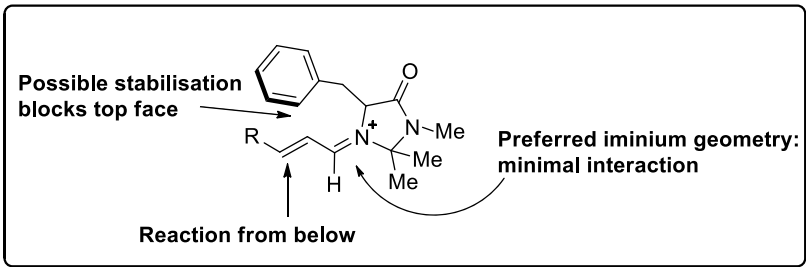


Figure 5.10: Activation mode of iminium ion.

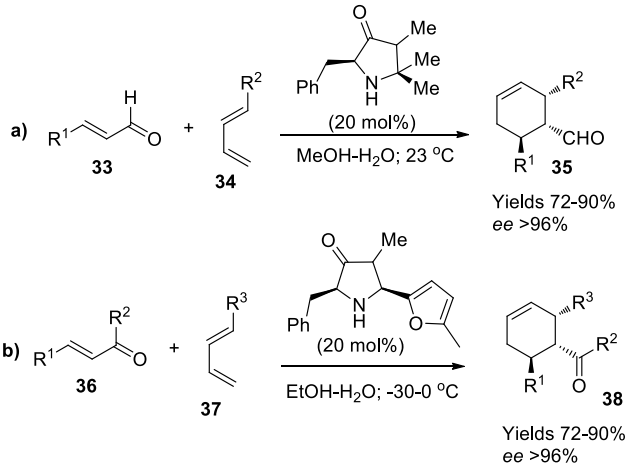


Figure 5.11: Iminium ion catalyzed reaction.

can be encompassed to enals in excellent yields and enantiomeric organic compounds. The unsaturated aldehydes are easily constructed from the derivatives of nitrone cycloaddition with activated enals and can be applied to produce a collection of substituted derivatives (Figure 5.12a) [55]. Preferably, a procedure that includes C–C bond development as a piece of the iminium and enamine-mediated stages would be a dominant technique in synthesis. In this manner, various heterocycles can be included in the iminium-activated enal and ensuing enamine captured with a chlorinating mixture to produce effective aldehyde building blocks. Jorgensen's group investigated a tandem procedure containing C–S and C–N bond development, providing chiral amino thiols that can be easily transformed into medicinally important derivatives (Figure 5.12b) [57]. A consequent oxidation procedure has been reported by employing a mixture of urea-hydrogen peroxide with an enal and secondary amine catalyst to give the epoxides. Marigo and coworkers described an operationally simple epoxidation method that performed well for a series of starting substrates offering high yields and enantiomeric excess (Figure 5.12c) [58].

5.2.3 Hydrogen-bonding catalysis

Numerous asymmetric catalyst procedures indicated that activation of starting precursors and the establishment of the transition state might happen *via* well-specified hydrogen-bonding interactions [59–62]. Wenzel and coworkers described that thiourea catalysts could be applied for enantioselective hydrogen-bonding catalysis [63, 64], utilizing its capability to activate electrophiles similar to direct Lewis acid activation. Instead of employing metal-coordinate carbonyl lone pair of electrons, it depends on a

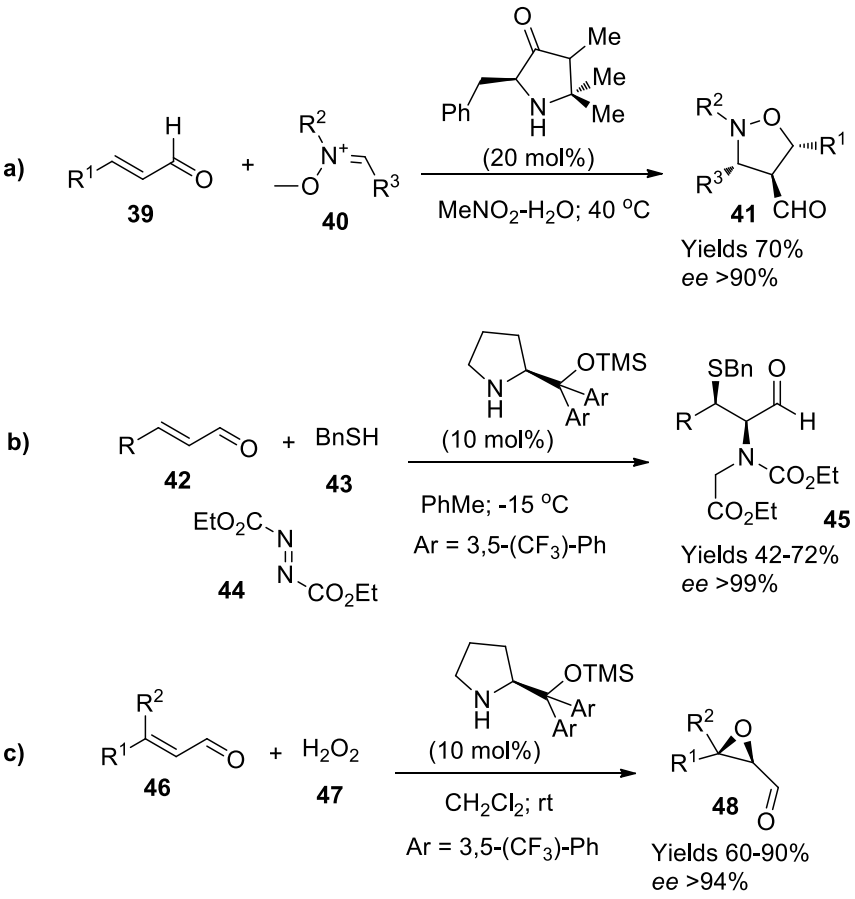


Figure 5.12: Iminium ion catalyzed reaction.

hydrogen bond to improve activation and produce a chiral environment across the electrophilic counterparts [65–68].

Gergelitsova et al. [69] described the synthesis of thiourea-phosphine catalysts for the enantioselective reaction (Morita–Baylis–Hillman) of acrylates with aldehydes. Use of 10 mol% of thiourea catalyst in MTBE solvent performed well and offered good yields and excellent enantioselectivity of chiral esters at 25 °C (Figure 5.13a). In 2016, Isenegger et al. [70] developed the thiourea-tertiary phosphine as an ideal organocatalyst for the reaction of methyl acrylate with various aldehydes (Figure 5.13b). Aromatic and heteroaromatic aldehydes with varied functional groups offered high yields (83–98%) of ensuing allylic alcohol derivatives with excellent enantioselectivities (up to 94% ee).

Chiral diol molecules could be applied as H-bond donors to initiate aldehyde compounds of carbonyl groups for cycloaddition reactions. The conventional Diels–

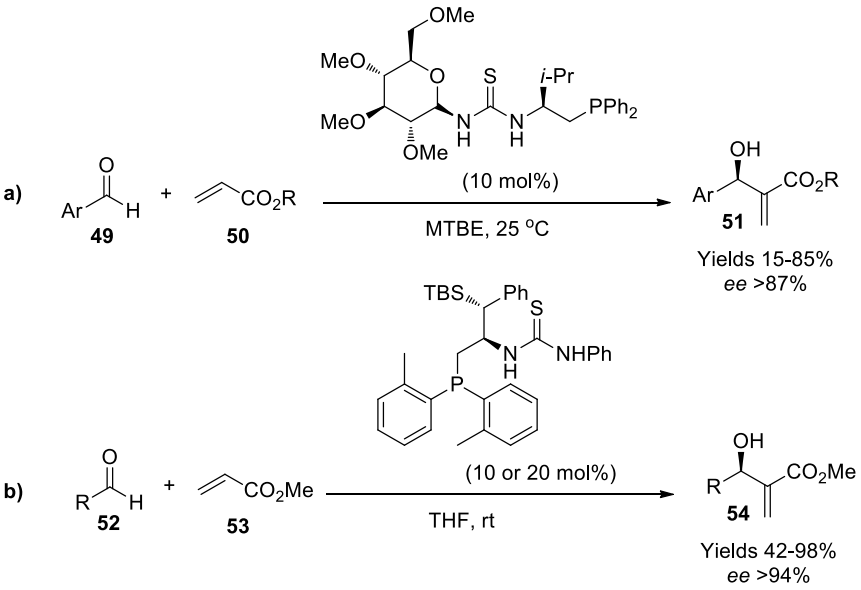


Figure 5.13: Thiourea-derived catalyzed reactions.

Alder reaction effectively catalyzed the generation of carbocyclic molecules with excellent enantioselectivity [71]. Binol-derived catalysts also promote the Baylis–Hillman type reactions in the mixture with aldehyde or imine, delivering valuable enantioselective derivatives (Figure 5.14a and b) [72, 73].

Vachal's group has established various chiral thioureas as organocatalysts to activate imines via hydrogen bonding to the nitrogen atom. Various suppressed nucleophiles can be included in these electrophiles in great enantiomeric excesses (Figure 5.15a) [74]. These thiourea-derived catalysts have supple properties as for asymmetric organic synthesis. Additionally, the cranialization of ketones was also achieved in excellent yields and good enantiomeric excesses comparably using other thiourea-derived catalysts (Figure 5.15b) [75]. Vachal's outcomes have motivated others to examine thiourea catalysis. Subsequently, indole reacted with nitroalkenes reaction has been described in the presence of thiourea catalyst and offered good yields and excellent enantiomeric excesses products (Figure 5.15c) [76].

5.2.4 Phase transfer catalysis

Raheem has established a unique organocatalyst, which activates the substrates leading to superb enantioselective adducts and produces oxocarbenium and *N*-acyl-iminium ions [27, 77]. Guanidine and their corresponding salts are well established as a strong base. Free guanidine shows double performance, Brønsted basicity, and H-bond

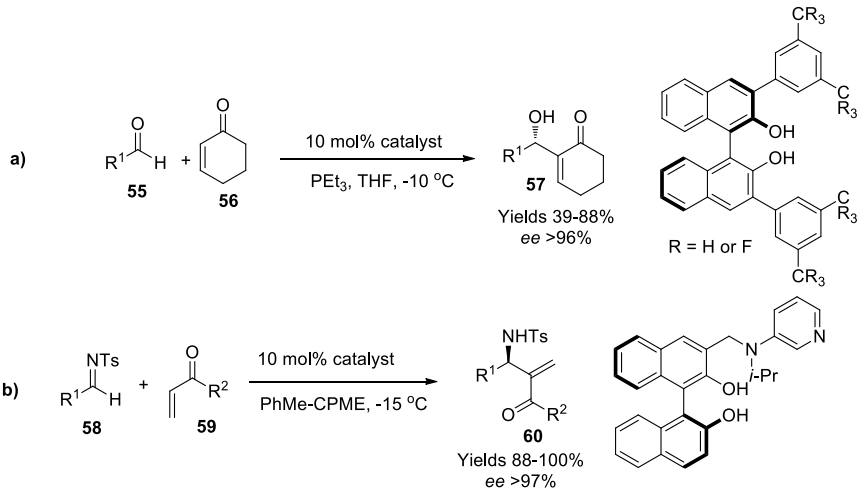


Figure 5.14: Binol-derived catalyzed reaction.

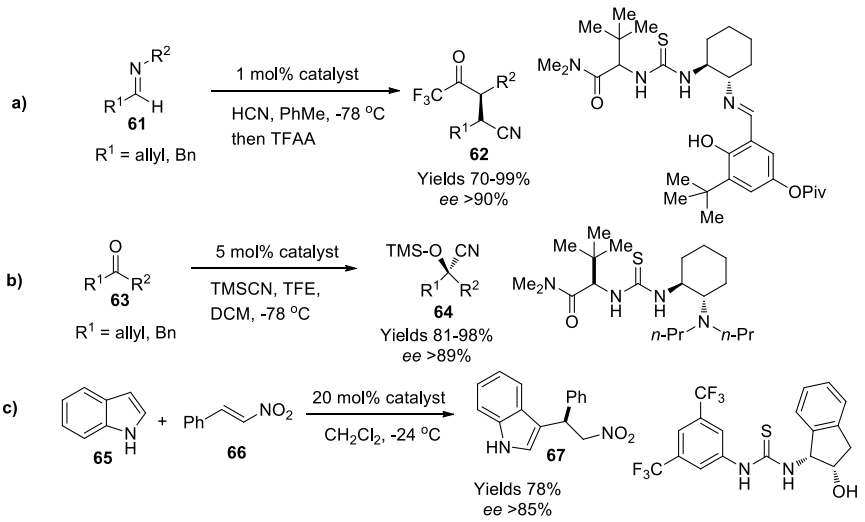


Figure 5.15: Thiourea-derived catalyzed reaction.

accepting and donating abilities [78]. Low Brønsted acidity of guanidinium salts also exhibited H-bond donating ability (Figure 5.16).

The use of phase-transfer catalysts for the synthesis of asymmetric alkylation is well-recognized. Kita and coworkers [79] investigated phase-transfer pentacyclic guanidinium salts for enantioselective alkylation with high enantiomeric excess and yields (Figure 5.17a). The guanidinium catalyst reacts with various alkyl halides through glycinate Schiff base state, which leads to the alkylation product. Leow et al. described

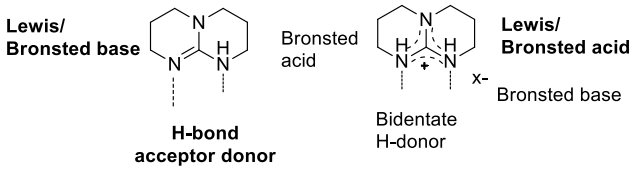


Figure 5.16: Hydrogen bond donor/acceptor of guanidine.

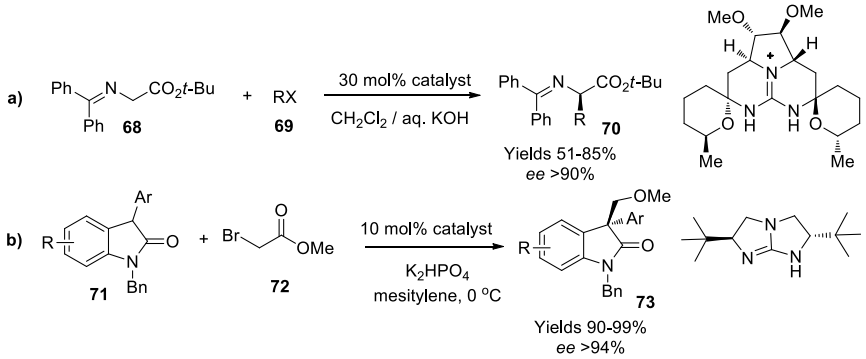


Figure 5.17: Guanidine-derived catalyzed reaction.

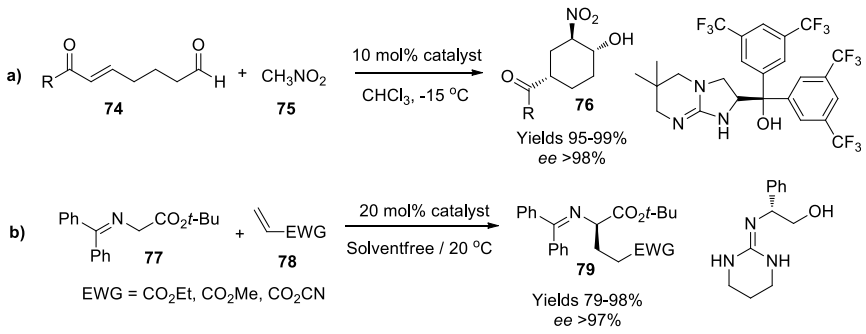


Figure 5.18: Guanidine-derived catalyzed reaction.

bicyclic guanidinium as a phase-transfer chiral organocatalyst for enantioselective alkylation to synthesize 2-oxiindole derivatives (Figure 5.17b) [80, 81]. The change in position and substituents on the phenyl ring did not affect the enantioselectivity of the final products.

Henry-Michael type reaction has developed by Dia and coworkers, which is the highly stereoselective tandem reaction. Guanidine catalyst was used to synthesize trisubstituted cyclohexanols with an excellent enantiomeric excess (Figure 5.18a) [82]. Ishikawa et al. have reported the guanidine as an organocatalyst to accelerate the

Michael-type reaction between a variety of Michael acceptors and glycinate substrates under neat conditions to afford superb enantioselective products (Figure 5.18b) [83].

5.3 Conclusions

Organocatalysis has evolved as an attractive option holding a wide assortment of valuable improvements relative to metal catalysts. Due to the easy accessibility of catalysts, low toxicity, high purity, and simple control of the chemical reactions, it has become a desirable procedure to generate small organic molecules. There is an upsurge of this asymmetric catalytic approach and employed in several synthesis domains. Indeed, the design and invention of numerous innovative methods and techniques in the forthcoming times will broaden its applications. Many novel enantioselective organocatalysts have been developed to synthesize enantio-selective molecules in excellent yields. The activation mode of organocatalysts such as proline, proline derivatives, thioureas, and Bronsted acids or bases has been established in different organocatalytic reactions. This work highlights the successive advances with organocatalysts in asymmetric organic synthesis, leading to future innovations.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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6 Organo-catalysis as emerging tools in organic synthesis: aldol and Michael reactions

Abstract: Organocatalysis has occupied sustainable position in organic synthesis as a powerful tool for the synthesis of enantiomeric-rich compounds with multiple stereogenic centers. Among the various organic molecules for organocatalysis, the formation of carbon–carbon is viewed as a challenging issue in organic synthesis. The asymmetric aldol and Michael addition reactions are the most significant methods for C–C bond forming reactions. These protocols deliver a valuable path to access chiral molecules, which are useful synthetic hybrids in biologically potent candidates and desirable versatile pharmaceutical intermediates. This work highlighted the impact of organocatalytic aldol and Michael addition reactions in abundant solvent media. It focused on the crucial methods to construct valuable molecules with high enantio- and diastereo-selectivity.

Keywords: aldol; asymmetric synthesis; enantioselectivity; Michael addition; organocatalysis.

6.1 Introduction

Over the years, the development of new chemical conversions permitting efficient and practical syntheses of complex and small organic structures has been the focal objective for synthetic organic chemists in both academia and the pharmaceutical industry [1, 2]. For this persistence, a plethora of organic reactions by applied organocatalysis that is consent the stereocontrolled synthesis of medicinal important candidates [3, 4]. Over decades, attention on organocatalysis has gotten an incredible upsurge in popularity in the chemical science field [5–7]. The advances on asymmetric catalysis with the practice of complex/small organic scaffolds as chiral catalysts plug a

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break between enzyme- and metal-catalysis [8–11]. The considerable attention in these types of catalysis is grown by additional appealing advantages which include stability, nontoxic, easy handling, less expensive, and ready availability of the catalysts, and the panorama of completing reactions under solvent and in air conditions are less sensitive when compared to the metal-catalyzed reactions [12–15].

In recent years, enantioselective synthesis in the presence of organocatalysts have been raised in popularity in organic synthesis for the construction of carbon–carbon (C–C) and carbon–heteroatom (C–X) bond organic reactions [16–18]. Many of the organocatalysts that catalyzed the reactions with advanced protocols have exhibited enantioselective isomers and consequently, the usage of organocatalysts and their derivatives allows finding out the cause of chirality in organic reactions [19, 20]. These organic catalysts framework showed by activating starting materials over covalent- or noncovalent-interactions. These interactions outcomes significantly enhance the rate of reaction and lead to stereoselective derivatives [21–24]. Several new concepts have been developed on asymmetric synthesis, particularly aldol and Michael additions allowing a broad range of effective transformations and an ideal approach for novel synthetic methods and new chiral catalytic systems [25–28]. Since the progress of organocatalysis, asymmetric aldol condensation has been broadly applicability of interest and lies in the viability of enantioselective synthesis of β-hydroxyderivatives over new C–C bond generation, which facilitates one or multiple stereogenic centers [29]. The β-hydroxy analogs are of great significance in the progress of potential pharmaceutical industrial applications [30]. Additionally, the synthetically viable and high diversity of chiral building blocks and the scope of donor and acceptor in Michael addition have been established. The unsaturated carbonyl compounds are attractive synthetic substrates due to their opaque number of reactive centers and their superb reactivity and are widely used in enantioselective Michael addition reactions [31, 32]. However, over the years considerable attempts have been built by several synthetic chemists to progress on organocatalysts catalyzed aldol and Michael reactions and novel asymmetric methodologies for the synthesis of bioactive scaffolds. Therefore, here, we discussed aldol and Michael's addition reactions in the organocatalysis space, valuable in synthesis in medicinally important molecules.

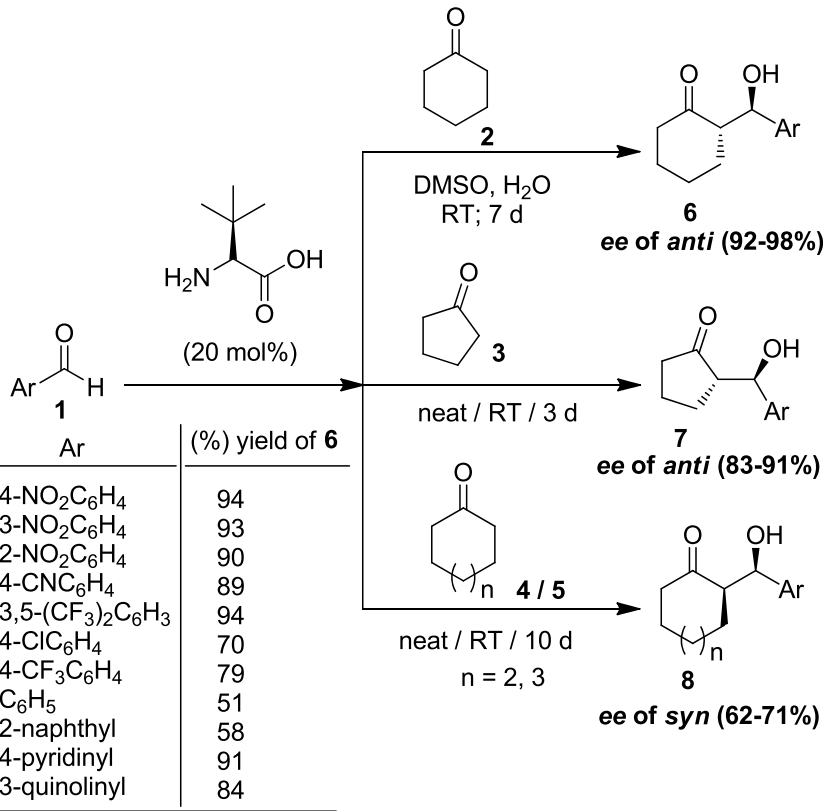
6.2 Enantioselective organocatalytic aldol reactions

The aldol condensation reaction signifies the most essential topic in advanced organic synthesis. Which is involves the two carbonyl molecules, results in a C–C bond β-hydroxy carbonyl compound generation and has been investigated in 1872 by Wurtz and Borodin [33–35]. The asymmetric aldol reaction has increased considerable interest and is often used for enantioselective C–C bond formation reactions. These structural analogs are established in several biologically potential intermediates and naturally ensuing molecules [36, 37]. In recent days, the aldol condensation asymmetric reaction

is widely engaged as a useful practice for the building of functionalized scaffolds with substantial biological activities.

6.2.1 Primary amines catalyzed aldol reaction

An efficient organocatalytic reaction was performed in the presence of a commercially available *L-t*-leucine in DMSO and water at room temperature for the synthesized asymmetric aldol reaction with *anti* isomers (Figure 6.1). A 20 mol% of catalyst loading was catalyzing the aldol condensation with various substituted aromatic and hetero-aromatic carbonyl compounds (**1**) and cycloketone (**2**) to provide the condensed aldol products (**6**) with outstanding yields in up to 92–98% *ee* for the excellent anti enantioselectivity and low diastereoselectivity (*syn*/*anti* = 1:9). Further explored the aldol reactions between various ketones (cyclopentanone (**3**), cycloheptanone (**4**), and cyclooctenone (**5**)) with benzaldehydes under neat conditions, which often displays



Ar	(%) yield of **6**
4-$NO_2C_6H_4$	94
3-$NO_2C_6H_4$	93
2-$NO_2C_6H_4$	90
4-CNC_6H_4	89
3,5-$(CF_3)_2C_6H_3$	94
4-ClC_6H_4	70
4-$CF_3C_6H_4$	79
C_6H_5	51
2-naphthyl	58
4-pyridinyl	91
3-quinolinyl	84

Figure 6.1: *L-t*-Leucine-catalyzed asymmetric aldol reaction.

deprived reactively, resulted in the aldol product (**7**) within high enantio- (>91% *ee*) and low diastereo-selectivities were obtained [38]. As reported outcomes revealed that, less than C7 cyclic ketones offered excellent anti enantioselectivity aldol products in the presence of *L-t*-leucine catalyst, whereas cycloheptanone or cyclooctenone resulted in the *syn* products (**8**). The cyclohexanone reaction was involved through the *s-trans*-enamine transition state; hence it produced the antiproducts [39]. The *L-t*-leucine catalyst having a *tert*-butyl group and it was influenced the stability of the enamines without decarboxylation, and which was further supported by molecular mechanics calculations [38].

Another *anti*selective direct asymmetric aldol reaction was described by Wu et al. [40]. The aldol reaction was catalyzed by threonine-based amino acid as an organo-catalyst (5 mol%), and aldol reaction was carried out between a cyclohexanone (**9**) and different benzaldehydes (**10**) in a water solvent medium at room temperature with excellent activity and good enantioselectivity and diastereoselectivity (**11**). The amino acid organocatalyst as a chiral analog, because of the OH moiety allows varieties of hydrophobic interactions with both acyl, and alkyl. The reported outcomes showed that the formation of *syn*- or *anti*-aldol products, which could be controlled by the acid additive. The threonine catalyst could enhance the reaction rate to give the aldol derivatives in excellent yields (83–99%) with a *dr* value of >99:1% (*anti*/*syn* ratio) and excellent enantioselectivity (>99% *ee* of the *anti*-isomer) (Figure 6.2). Further, the reaction conditions were explored with acyclic ketones and cyclopentanone as aldol donors. While the aldol donor cyclopentanone offered the significant yield (92–99%) of products with high *ee* >98% for the anti isomer and *dr* ratio 62:38 (*anti*/*syn*). Whereas acyclic ketones (acetone and hydroxy acetone) gave the *syn*-isomer (>99% *ee*) products with excellent yields (92–97%), and it required a longer reaction time than the cyclic ketones. In addition, the organocatalyst was recovered easily and reused six successive

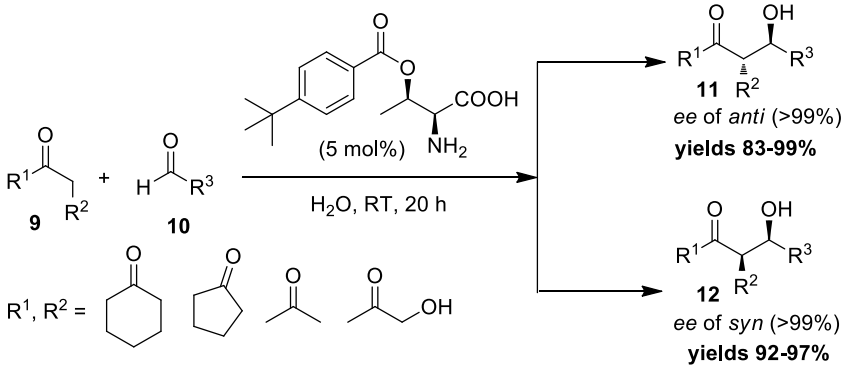


Figure 6.2: Threonine-based catalyzed asymmetric aldol reaction.

runs without loss of its catalytic activity and presented enantioselectivity being preserved with a similar level up to 98% *ee* of *anti*selective products.

The catalyzed stereoselective asymmetric aldol reaction of isatin (**13**) and acetaldehyde (**14**) by using quinine–amine organocatalyst and benzoic acid in THF solvent (Figure 6.3). A loading of 10 mol% of quinine–amine catalyst along with benzoic acid as a cocatalyst, which could also participate in the catalyzation of the aldol condensation and offered significant yields (87–97%) of *anti*-isomer aldol adduct (**15**) with a higher enantiomeric excess (*ee*, up to >93%) [41]. In addition, this protocol was explored with different substrates such as propanal, acetone, and cyclohexanone as an aldol donor. While the use of propanal and cyclohexanone precursors were giving excellent yields (93 and 98%) of desired *syn*-product (48% *ee* and 25% *ee*) and significant diastereoselectivity (*dr* 61:39 and *dr* 97:3). Whereas, acetone substrate was offered 96% of *anti* isomer aldol adduct with 61% *ee* of enantioselectivity. When acetaldehyde was employed in the presence of cinchona alkaloids as a primary amine catalyst, the cross-aldol product was obtained in a highly enantioselective manner reported by Perera et al. [42]. Notably, acetaldehyde could also undergo a straight aldol reaction as a donor in the presence of a quinine–amine catalyst with a significant level of enantioselectivity.

Wynands et al. described the amino tetrazole–glycosyl as an organocatalyst for direct asymmetric aldol reaction from a variety of aromatic aldehydes (**16**) and acetone (**17**) (Figure 6.4) [43]. The 10 mol% of catalyst promoted the aldol reaction at 60 °C for 2 h and gave good yields (34–99%) and excellent enantioselective (*ee*, >98%) aldol adduct (**18**). Further explored in the Density-functional theory (DFT) studies, the ideal transition structure includes the attack of the antienamine on the aldehyde of *Re*-face in an impending angle of –60° and displays the extended C–C bond while the catalyst-tetrazole proton is slightly moved and drives to the *R*-enantiomer.

Shim et al. [44], have explored the chiral diphenylethylenediamine (DPEN) catalyzed the direct aldol reaction. The aldol adducts (**21**) were obtained from with

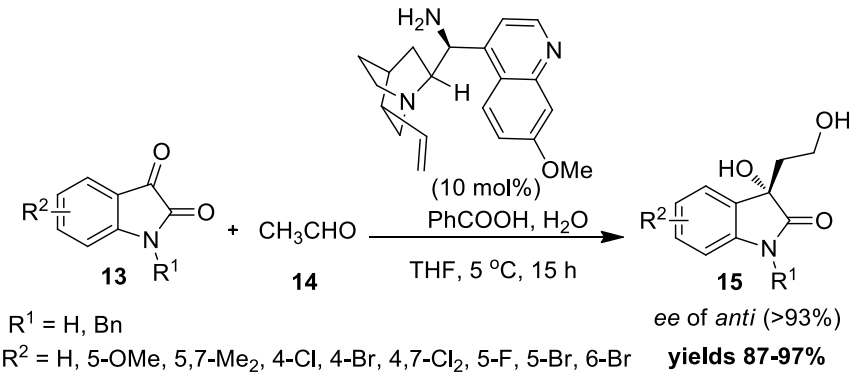


Figure 6.3: Quinine–amine-catalyzed aldol reaction.

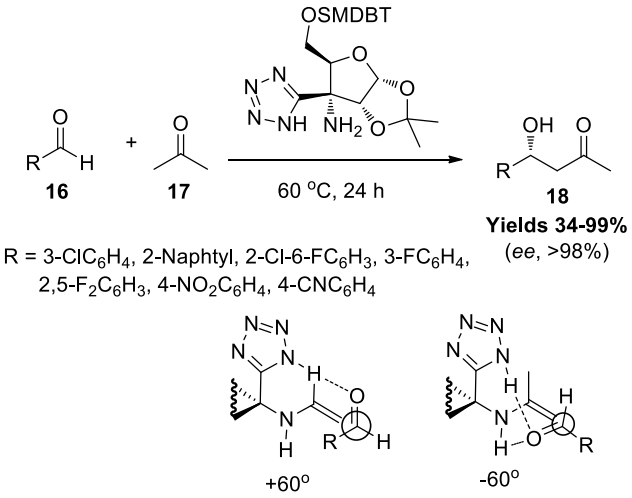
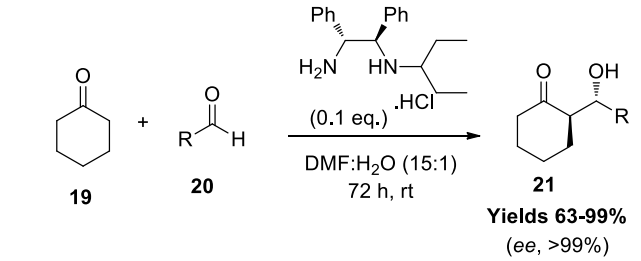


Figure 6.4: Tetrazole-based catalyst-catalyzed aldol reaction.

cyclohexanone (**19**) with various aldehydes (**20**) in mixture of dimethylformamide (DMF) and water (15:1) solvents at room temperature. Use of 0.1 eq. chiral DPEN catalyst gave a superior performance and afforded the high yields (63–99%) of anti isomer derivatives with high enantioselectivity (*ee* >99%) for 72 h reaction time (Figure 6.5). The DPEN catalyst of primary amine proceeded through enamine and iminium intermediates to offer the enantioselectivity scaffolds. As reported results revealed that the *ortho*-substituent substrates have facilitated greater stereoselectivities than *para*-substituents due to the stereoscopic effect was augmented.

Zong and coworkers [45] have reported the *N, N*-disubstituted chiral diamine as an organocatalyst and used for the synthesis of aldol adduct and alcohol derivatives (**24**). The asymmetric aldol reaction was carried out between the trifluoromethyl ketones (**22**) and different aliphatic ketones (**23**). Use of 5 mol% of organocatalyst in TsOH and toluene solvent offered the best catalytic activity and gave significant yields (75–98%) of alcohol derivatives with excellent enantioselectivity (*ee*, up to 95%) at 0 °C for 24 h (Figure 6.6). Further explored the high electron-withdrawing group (CF_3) of ketone substrate was replaced with CF_2Cl group, which is less electron-withdrawing group offered the less yield (75%) and enantioselectivity (*ee*, 81%) products. The reaction proceeded with the enamine intermediate with aliphatic acetones in the presence of chiral catalyst and which is situated transition state on the *Re*-face of trifluoromethyl ketones were more favored to give the (*s*)-derivatives, due to less steric repulsion.

Another chiral diamine organocatalyst (1,2-cyclohexanediamine; DACH) and aldol reaction was described by Li and coworkers [46]. The aldol products (**27**) were obtained from the reaction of cyclohexanone (**25**) and various aryl and heteroaryl aldehydes (**26**) in ethanol at room temperature. Using of 10 mol% of organocatalyst performed



R = 4-ClC_6H_4, 3-ClC_6H_4, 4-$F_3CC_6H_4$, 2-$F_3CC_6H_4$, 4-$MeOC_6H_4$
4-MeC_6H_4, 4-$O_2NC_6H_4$

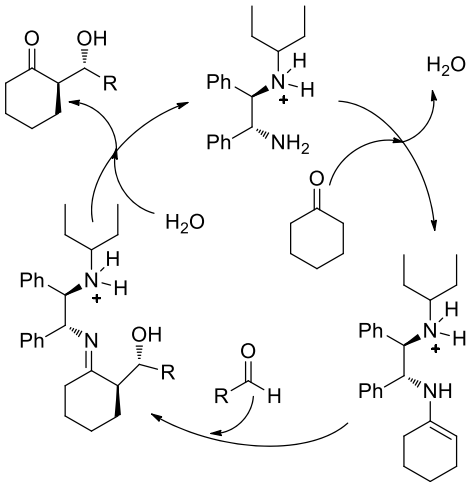


Figure 6.5: Chiral diamine catalyzed aldol reaction.

effectively in the presence of procatalyst TFA and offered significant yields (63–93%) of *anti*-isomer aldol products with high enantioselectivity (*ee* >99%) (Figure 6.7). Electron withdrawing groups of aldehydes offered high yields of products than the electron-donating group substituents. The catalyst phenyl ring involved on noncovalent π–π interaction with aldehyde substrates (**28**), which makes the enamine intermediate more stable, to gives the (*s*)-aldol products [47].

6.2.2 Secondary amines catalyzed aldol reaction

Proline is a secondary amine, and it displays improved basicity and nucleophilicity in comparison to various amino acids primary amines. Among C–C bond developing, the aldol reaction is the greatest studied proline-catalyzed asymmetric method. Many proline derivatives have been utilized as catalysts for enantioselective aldol reactions, which progressed in outstanding diastereo- and enantio-selectivities molecules. The

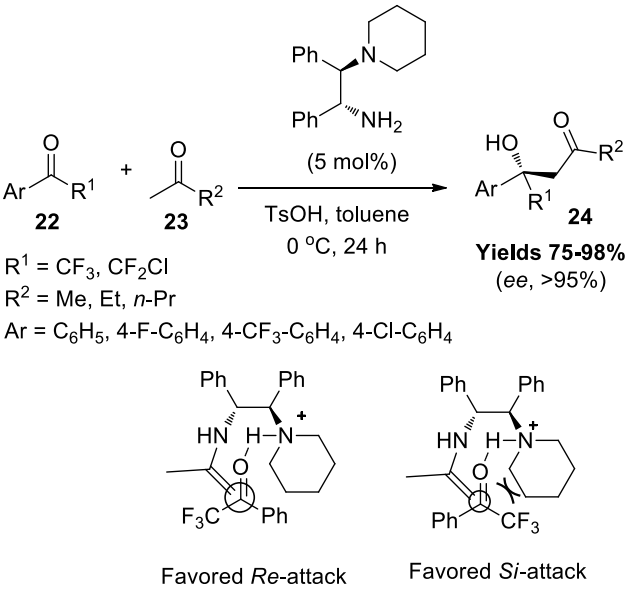


Figure 6.6: Chiral diamine catalyzed aldol reaction.

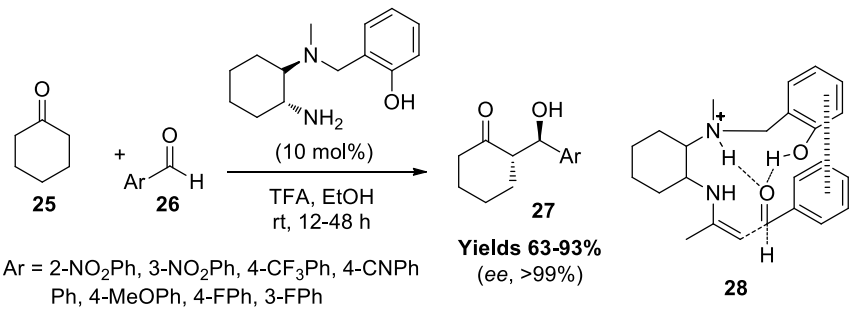


Figure 6.7: Chiral diamine catalyzed aldol reaction.

catalytic production of asymmetric enolate counterparts immensely contributed to the growth of organocatalysis. There have been several subsequent reports of catalytic reactions *via* enamines have been established.

List and Barbad reported an intermolecular procedure with secondary amine catalysis *via* enamines with acetone (**29**) and aldehydes (**30**) to give the highly enantioselective products (**31**). The proline catalyzes asymmetric aldol reaction processed in dimethyl sulfoxide as an optimized solvent, which was important to the progress of organocatalysis (Figure 6.8) [48, 49]. Later Phihko and his research group described the addition of water in organic media (DMF), which was an improved rate of reaction and

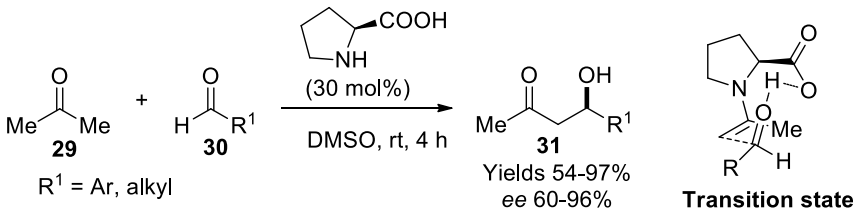


Figure 6.8: Proline catalyzed aldol reaction.

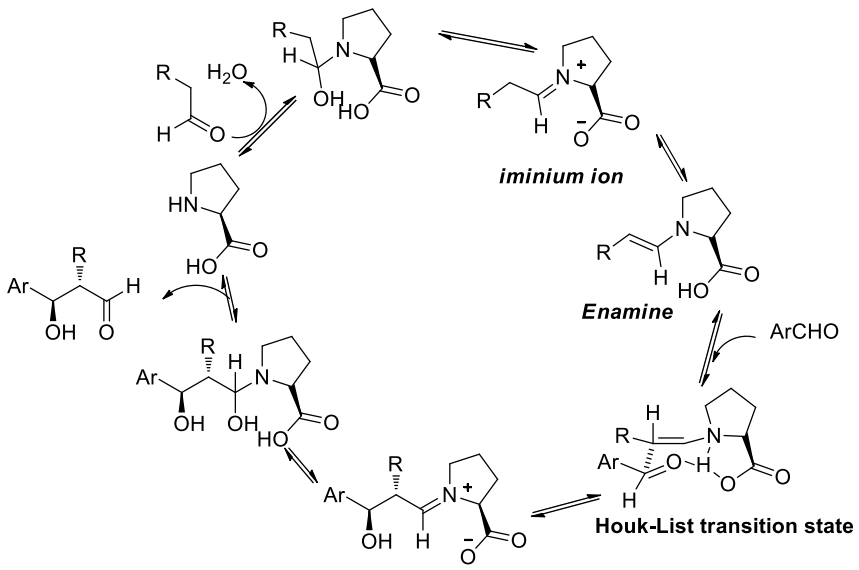


Figure 6.9: The proposed mechanism of proline-catalyzed aldol reaction.

the yields of aldol adduct with good enantioselectivity [50]. The proline catalyzed aldol reaction involved through the Houck–List transition state model by enamine catalysis process, and it offers enantiomerically enriched aldol derivatives, which is further supported by DFT studies (Figure 6.9) [51].

A remarkable extension of this procedure was described by Northrup and co-workers, which explained the cross-aldehyde aldol coupling [52, 53]. A necessity of this chemical reaction is that the carbonyl group of aldehydes (**32**,**33**) could be specified as donor or acceptor. This clearly shows one aldehyde can develop an enamine (donor), and the other can behave as the acceptor. Use of 10 mol% of organocatalyst offered 75–88% of the yield of products (**34**) with good enantioselectivity (*ee*, 99%) in dimethylformamide medium (Figure 6.10).

A novel organocatalyst, urea linked at C-4 potion of proline has been developed by Bhati et al. [54]. The catalytic activity of this catalyst was explored for the synthesized of

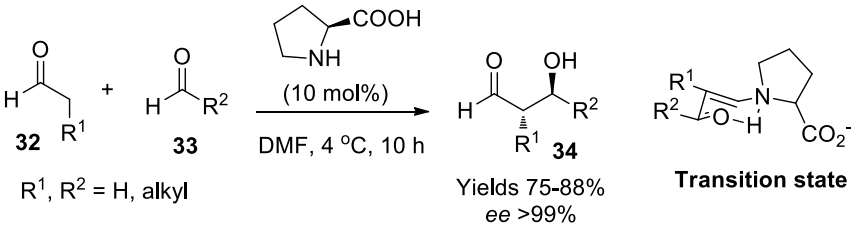


Figure 6.10: Proline catalyzed aldol reaction.

asymmetric aldol reaction. The condensation reaction was carried out between the cyclohexanone (**35**) and various aromatic aldehydes (**36**) in a water medium at 25 °C. A small catalyst loading (2 mol%) was performed effectively and gave excellent yields (55–99%) of aldol product (**37**) with high enantioselectivity (*ee*, 99%) and *anti:syn* ratio (up to 96:4) (Figure 6.11). Recyclability is the advantage of this protocol; the organocatalyst was stable up to seven times without noticeable loss of its activity. The urea-linked proline catalyst is involved in intramolecular host–guest interaction with urea and amino acid skeletons.

Han and coworkers [55] synthesized the hydroxysilanes (**40**) in the presence of hydroxyproline organocatalyst, which was obtained from the reaction of silyl glyoxylates (**38**) and different aldehydes (**39**) in DMF solvent at room temperature. Twenty mole percent of catalyst proved the excellent catalytic activity and offered good yield (44–65%) of corresponding products and high enantioselectivity (*ee*, up to 99%) (Figure 6.12). Onside of silyl glyoxylate having different ester functional groups were also offered superb results and while the different silicon compounds such as trimethylsilyl (TMS), *tert*-butyl-dimethylsilyl (TBS), and triethylsilyl (TES) were also well tolerated. Whereas triisopropylsilyl (TIPS) attached silyl glyoxylate substrate did not proceed with the reaction. The organocatalyst involved the reaction through enamine intermediate and transition state; the carbonyl group directly attached to silicon and can be activated by coordination through hydrogen bond (**41**).

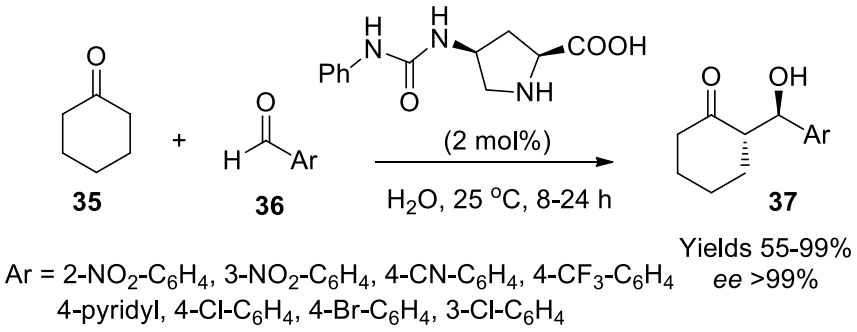


Figure 6.11: Proline-urea catalyzed aldol reaction.

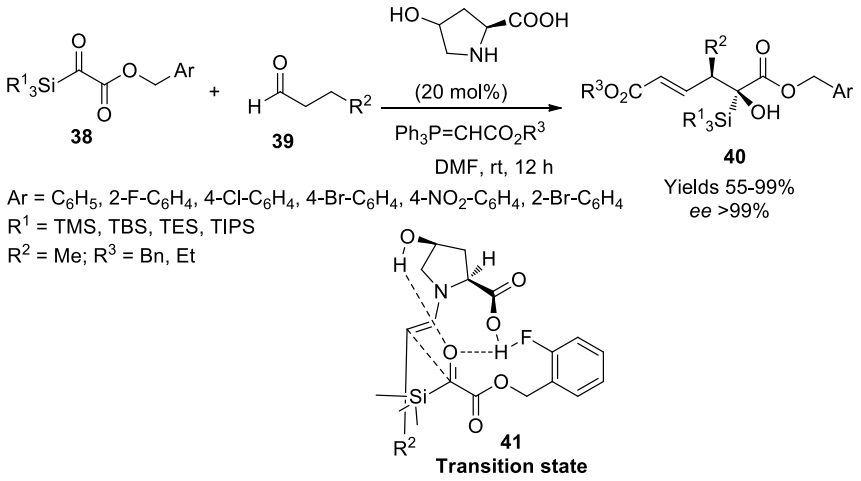


Figure 6.12: Hydroxyproline catalyzed aldol reaction.

Cho and Kim [56] reported the asymmetric aldol reaction in the presence of L-proline and cocatalyst salt of iodine isothiouronium. The hydroxy derivatives (**44**) were obtained from the reaction between the cyclohexane (**42**) and various aldehydes (**43**) under solvent-free conditions. Use of 15 mol% of chiral catalyst showed excellent catalytic activity with 10 mol% of cocatalyst (isothiouronium iodide) to gives the high yields (47–90%) of corresponding derivatives with excellent stereoselectivities (*ee* >99% and 93:7 *dr*) at 5 °C for 96 h reaction time (Figure 6.13). Unsubstituted aldehyde gave lower yields of the aldol adduct. The chiral catalyst and cocatalyst have involved the reaction in Zimmerman–Traxler transition state (**45**) through enamine intermediate.

Castaneda et al. [57], have described the *s*-proline catalyzed asymmetric *syn*-aldol reaction. The aldol condensation reaction was carried out between the cyclic ketones (**46**) and different aldehydes (**47**) in the presence of cocatalyst guanidinium salt under solvent-free conditions. The protocol offered the good stereoselective derivatives (**48**) up to 89:11 *dr* (*syn:anti*) and 98% *ee* with excellent yields (86–98%) by applied 10 mol% of catalyst and 15 mol% of co-catalyst at 3 °C for 120 h reaction time (Figure 6.14). The syn-diastereoselective exhibited reaction involved the enamine-based catalytic cycle with the carbonyl group of cyclic ketones.

6.2.3 Miscellaneous catalysts aldol reaction

Thorat et al. [58], reported the stereoselective synthesis of aldol adducts by applied pyrrolidine-based sulfonamide organocatalyst. The aldol reaction was carried out between the different aromatic aldehydes (**49**) and chloroacetone (**50**) in an ethanol

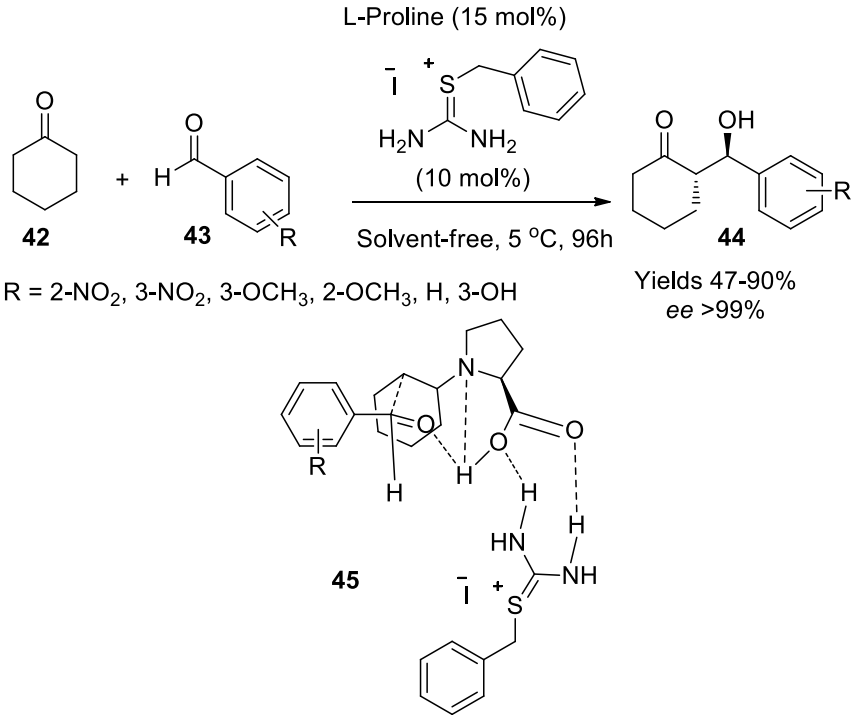


Figure 6.13: Proline catalyzed aldol reaction.

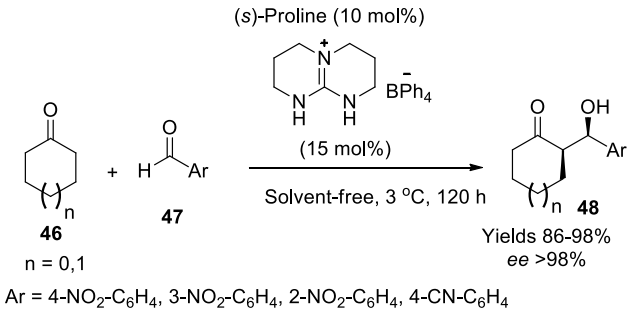


Figure 6.14: Proline catalyzed aldol reaction.

medium. Use of 15 mol% of pyrrolidine catalyst and along with cocatalyst triethylamine gave superior results and offered excellent yields (73–92%) of *anti*-selective hydroxy ketones (**51**) with high enantioselectivity (*ee*, >92%) (Figure 6.15). The chiral catalyst has also proved to synthesize the Knoevenagel condensation derivatives. The chiral organocatalyst sulfur from the sulfonyl group promotes by the creation of van der Waals interaction [59, 60], and enol strikes the *Re*-face of the aldehyde carbon,

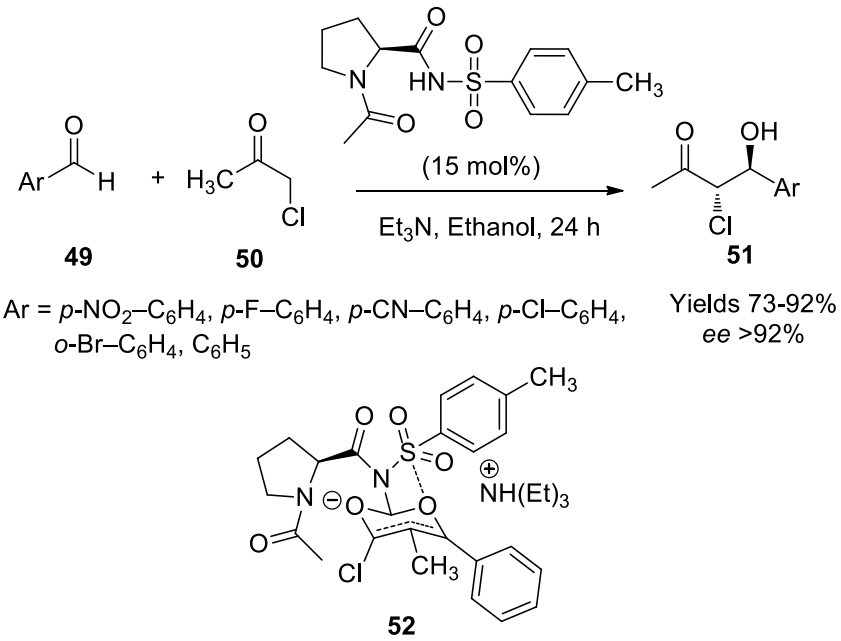
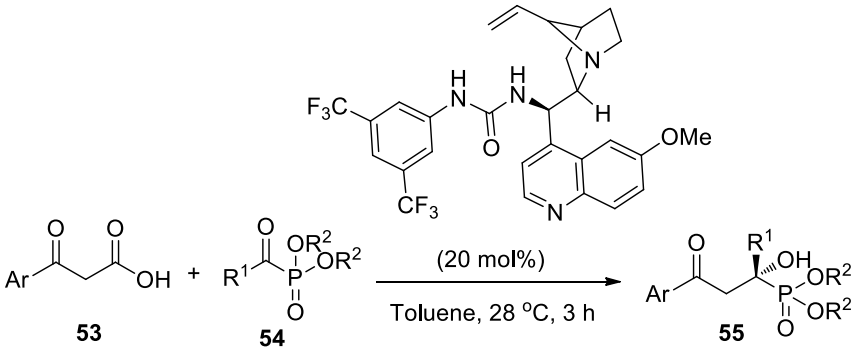


Figure 6.15: Pyrrolidine-based catalyst, catalyzed aldol reaction.

which precedes the generation of the transition state (**52**), and it provides the *anti*-selective derivatives.

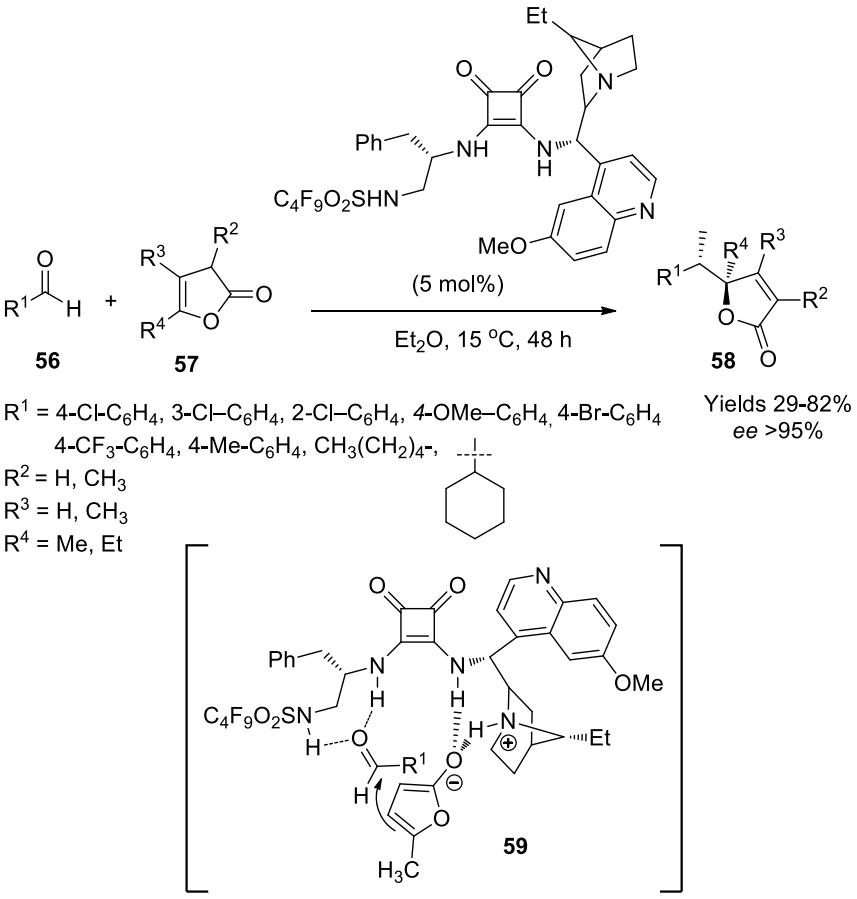
Vamisetti and coworkers [61] have reported the novel organocatalyst, urea-based cinchonidine, which was used for synthesized the decarboxylative aldol reaction. The aldol product hydroxy phosphonates (**55**) were obtained from the reaction of *β*-ketoacids (**53**) and *α*-ketophosphonates (**54**) in a toluene medium. Use of 20 mol% of organocatalyst performed effectively and gave the significant yields (56–82%) of corresponding products and good enantioselectivity of up to 93% *ee anti*-isomers at 28 °C (Figure 6.16). Both electron-withdrawing and donating groups were well tolerated.

Another novel organocatalyst, squaramide–sulfonamide was developed by Sakai and coworkers [62]. The catalyst catalytic activity was examined for the synthesized aldol reaction of functionalized furanone derivatives (**58**). The aldol reaction was carried out between the varieties of aldehydes (**56**) and butenolides (**57**) in the presence of low catalyst loading (5 mol%) squaramide-sulfonamide catalyst in diethyl ether at 15 °C for 48 h reaction time. Excellent yields of products (29–82%) were obtained with high enantioselectivity 95% of *ee* (Figure 6.17). Aldehyde bearing aliphatic chain and cyclohexane ring substrates gave lower yields of aldol derivatives. The organocatalyst continues via the *Si* → *Re* transition state (**59**) prominent to the major *anti*-isomer aldol products.



Ar = C_6H_5, *p*-F–C_6H_4, *p*-Br–C_6H_4, *p*-OMe–C_6H_4
R^1 = CH_3, C_2H_5
R^2 = Me, Et, *i*-Pr

Figure 6.16: Urea-based catalyst, catalyzed aldol reaction.



R^1 = 4-Cl-C_6H_4, 3-Cl–C_6H_4, 2-Cl–C_6H_4, *4*-OMe–C_6H_4, 4-Br-C_6H_4
4-CF_3-C_6H_4, 4-Me-C_6H_4, $CH_3(CH_2)_4$-,
R^2 = H, CH_3
R^3 = H, CH_3
R^4 = Me, Et

Figure 6.17: Squaramide–sulfonamide catalyst, catalyzed aldol reaction.

Park and co-workers [63] have described the thiourea-based cinchona organocatalyst for the synthesized hydroxy thioester compounds (**62**). The aldol reaction was conducted between the various ketones (**60**) and malonic acid half-thioester (**61**) in a mixture of methyl *tert*-butyl ether (MTBE) and THF (1:1) solvents. Use of 30 mol% of organocatalyst showed superb catalytic activity and furnished the excellent yields (6–99%) of aldol adducts and up to 95% of *ee* enantioselectivity at –20 °C for 96 h reaction time (Figure 6.18). Ketone bearing 2-methyl group on the phenyl ring exhibited very low yields of the aldol product due to steric influence of the moiety, whereas, both aromatic and heteroaromatic ketones were well tolerated in this method.

Moles et al. [64], have described the novel organocatalyst, *N*-tosyl-binam-prolinamide, and its catalytic activity was investigated for the synthesized hydroxycarboxylic acid derivatives (**65**). The aldol products were obtained from the reaction of various ketones (**63**) and glyoxylic acid (**64**) in a water medium under 10 mol% of an organocatalyst and Me_3SiCHN_2 as a co-catalyst. The protocol was offered the high enantioselective up to 97% of *ee* antiisomers with good yields (17–90%) at 0 °C (Figure 6.19). Whereas aliphatic ketones offered the lower yields of the aldol adducts.

Konda and coworkers [65] have described the asymmetric aldol reaction by using cinchona–thiourea organocatalysts. The phenylglyoxal hydrates (**68**) were obtained from the reaction of various acetophenones (**66**) with unsaturated-keto esters (**67**) under THF medium at 0 °C. The use of 20 mol% of organocatalyst executed the best performance in terms of yields (70–99%) and reaction time (42 h). This protocol presented up to 91% of *ee* enantioselectivity *anti*-isomers (Figure 6.20) and the reaction proceeded through a favored transition state (**69**) and *Si–Si* attack, which leads to the major *anti*isomer products.

6.3 Michael addition reaction

Amid the different C–C bond establishment protocols, Micheal addition through 1,4-conjugation performs a considerable position in current organic reactions [66].

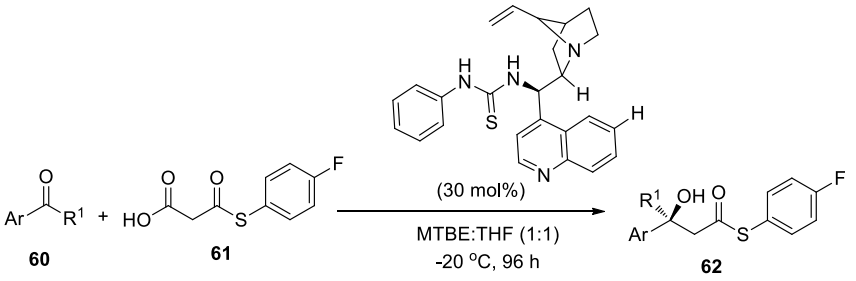


Figure 6.18: Thiourea-based cinchona catalyst, catalyzed aldol reaction.

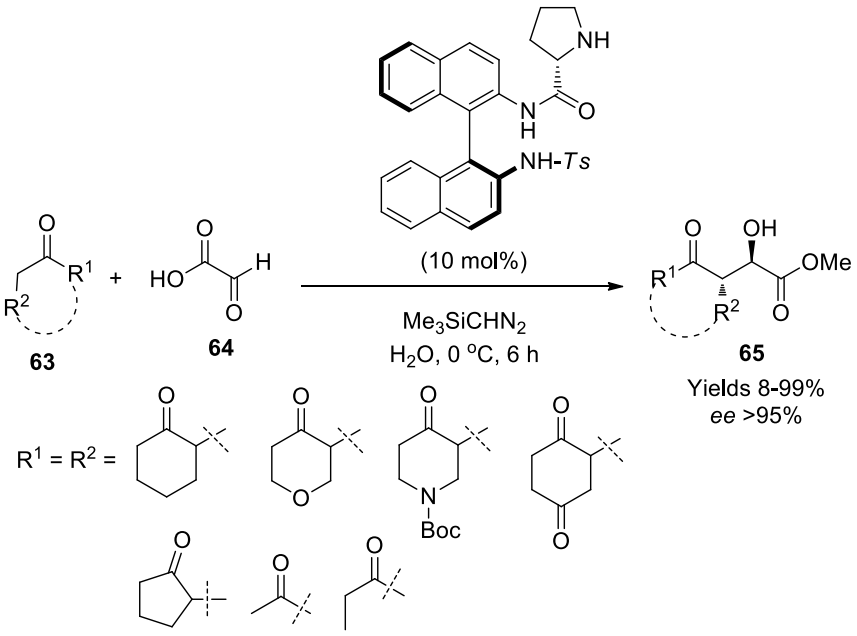


Figure 6.19: Binam-prolinamide catalyzed aldol reaction.

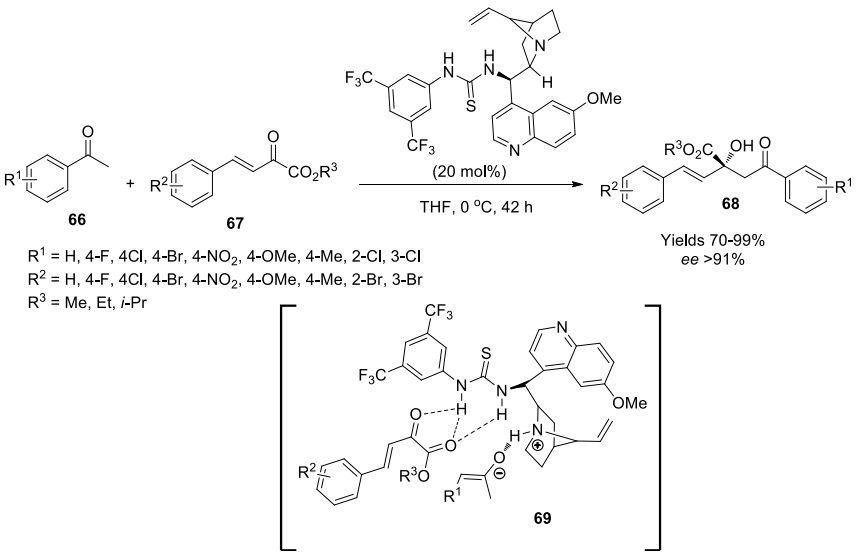


Figure 6.20: Cinchona–thiourea catalyzed aldol reaction.

Their deliberate significance is obvious by seeing that this addition reaction symbolizes commencing in different cascade tandem procedures [67]. Thus, many researchers have been established several catalytic asymmetric methodologies for this vital reaction, results in significant building blocks in organic synthesis [68].

Reddy et al. [69], described the bifunctional thiourea–cinchona as an organocatalyst, catalyzed the Michael addition reaction, The Michael addition reaction was carried out between the *p*-benzoquinone ditoluenesulfonimide (**70**) and various cyanoacetates (**71**) in toluene, to furnish the *p*-quinone diimides (**72**). Which were obtained with high (96% of *ee*) enantioselectivity and 92–97% of excellent yields at −30 °C for 12 h reaction time (Figure 6.21). The reported reaction continued with electrophile of quinone diimide is activated by the catalyst thiourea group of the catalyst, while the nucleophile of cyanoacetate moiety binds to the protonated quinuclidine amine group of the organocatalyst, to generate the transition state (**73**), which is supported by DFT studies and leads to the major anti-isomer products.

An efficient sulfa-Michael addition reaction was synthesized in the presence of cinchona dimer as an organocatalyst reported by Huang and coworkers [70]. The Michael addition was carried out between the reactions of fluoro-unsaturated esters (**74**) with aromatic thiols (**75**), to give the fluoroacrylate derivatives (**76**) with excellent yields (40–98%). The use of 10 mol% of catalyst has proved the successful transformation of corresponding product with syn-*isomers* (*dr* 94:6) of 82% of *ee* enantioselectivity at 0 °C (Figure 6.22).

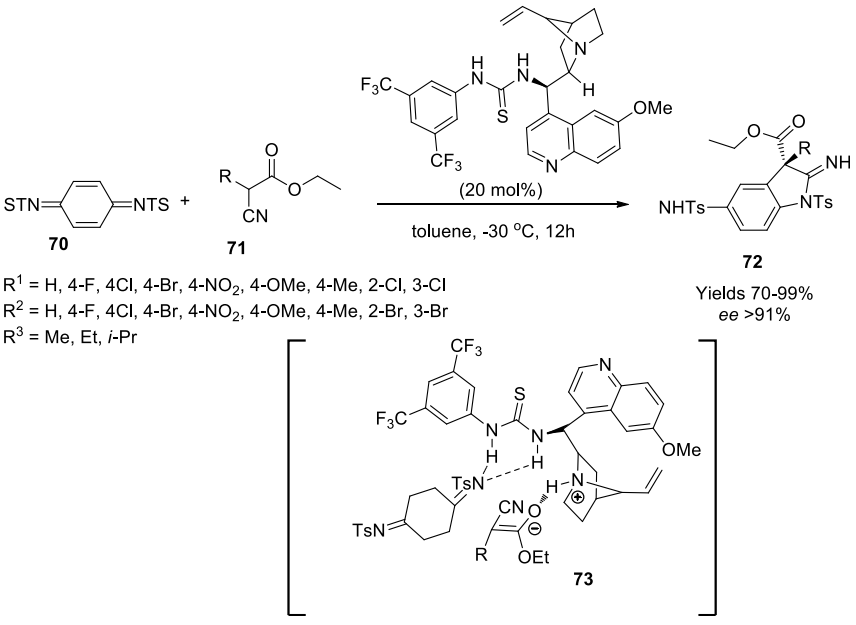


Figure 6.21: Cinchona–thiourea catalyzed Michael addition reaction.

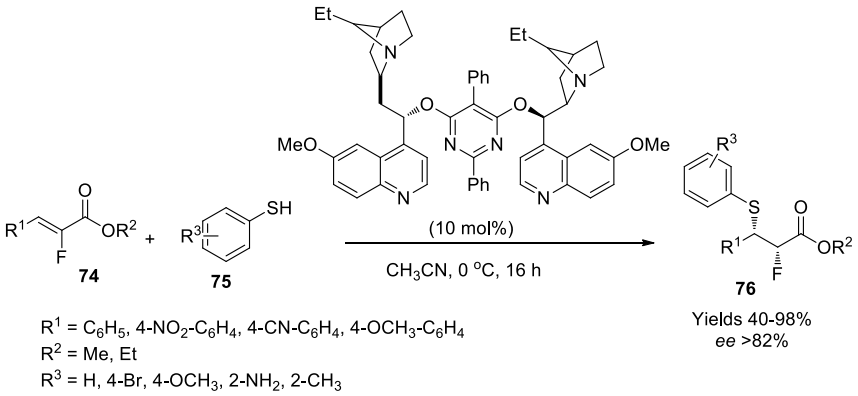


Figure 6.22: Bis-cinchona catalyzed Michael addition reaction.

Zhou and coworkers [71] reported the Michael and aza-Michael addition cascade reaction in the presence of organocatalyst, chiral squaramide. The *N*-Michael addition reaction carried out between the nitrobenzofuran/thiophene (**77**), and various functional groups substituted amino-chalcones (**78**) in dichloromethane solvent at room temperature. The small catalyst loading (20 mol%) was performed superior results with good yields (39–98%) and high enantioselectivity (up to 99% of *ee*) of quinoline derivatives (**79**) (Figure 6.23). Benzothiophene substrates gave fewer yield of products than

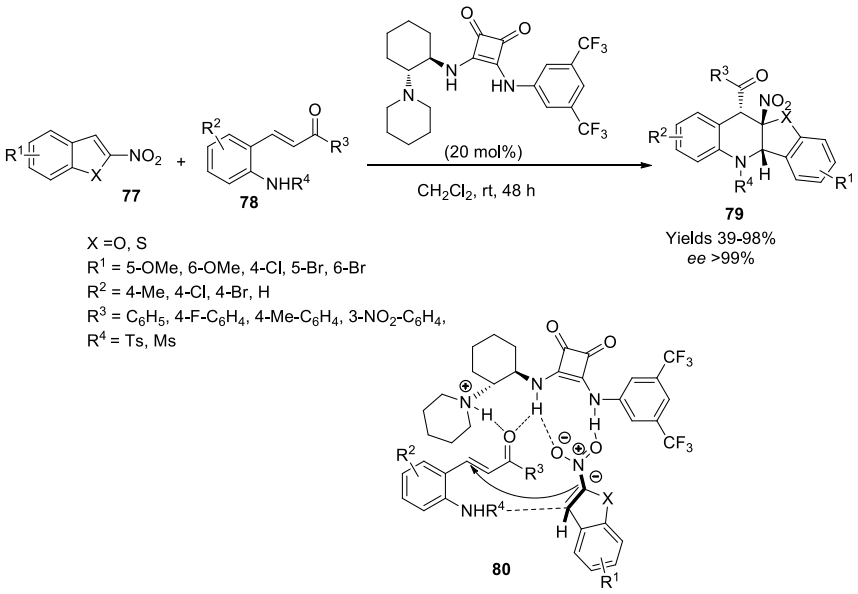


Figure 6.23: Squaramide catalyzed Michael addition reaction.

benzofurans. The Michael reaction proceeded through the transition state (**80**), nitrogen anion attack to the 2-nitrobenzofuran at C3-position from *Si*-face, which leads to the major *anti*-isomer.

Chen et al. [72], have investigated the novel organocatalyst bifunctional squaramide, which is used for the synthesis of chiral indolin-3-one molecules (**83**). The Michael addition reaction conducted the fusion of acetylindolin-ones (**81**) and unsaturated-ketoesters (**82**) in dichloromethane at 20 °C. Low catalyst loading (2 mol%) was shown superb catalytic activity to give the high yields (69–96%) of desired products with excellent enantioselectivity (*ee*, >99%) (Figure 6.24). Ethyl moiety substituted ketoester substrate did not perform the Michael addition reaction. The reported transition state (**84**) was achieved from squaramide catalyst amino group and acetylindolinone through hydrogen bonding interaction, which leads to the high stereoselective derivatives.

Gupta and Singh [73] have synthesized the quinine alkaloid organocatalyst for synthesized the vinylogous Michael addition reaction. The Michael reaction was carried out between the iminochromene (**85**) and butanolide (**86**) in the presence of 10 mol % of organocatalyst in DCM solvent at room temperature, to result in the 45–73% of *syn*-selective furanone–chromene–carbonitrile derivatives (**87**) (Figure 6.25). Both electron-deficient and electron-rich groups were allowed and presented superb yields of *syn*-products.

Chowdhury and coworkers [74] have developed the thiourea-based cinchona bifunctional organocatalyst, which is used for the synthesized Michael addition reaction. The functionalized spirooxindole analogs (**90**) were obtained from the reaction of isothiocyanate-oxindoles (**88**) with arylidene (**89**) substrates under 20 mol% of the

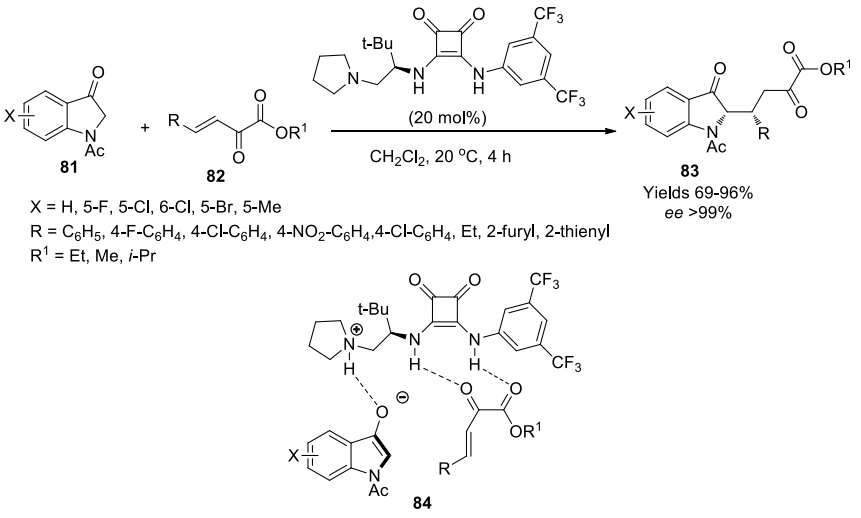


Figure 6.24: Squaramide catalyzed Michael addition reaction.

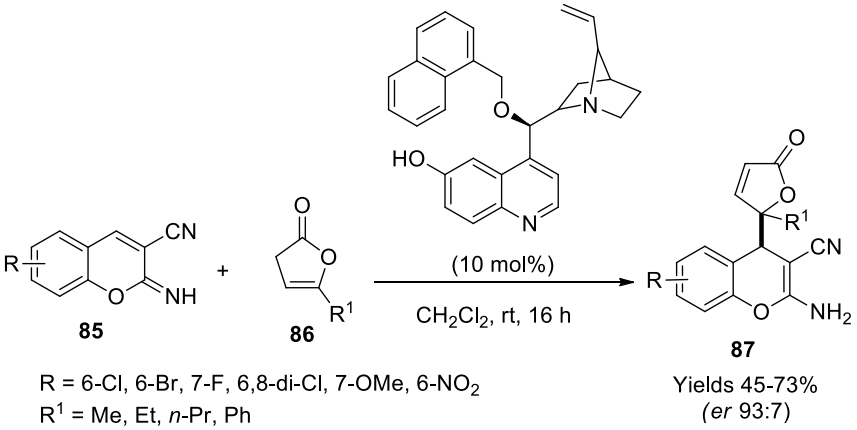


Figure 6.25: Quinine alkaloid catalyzed Michael addition reaction.

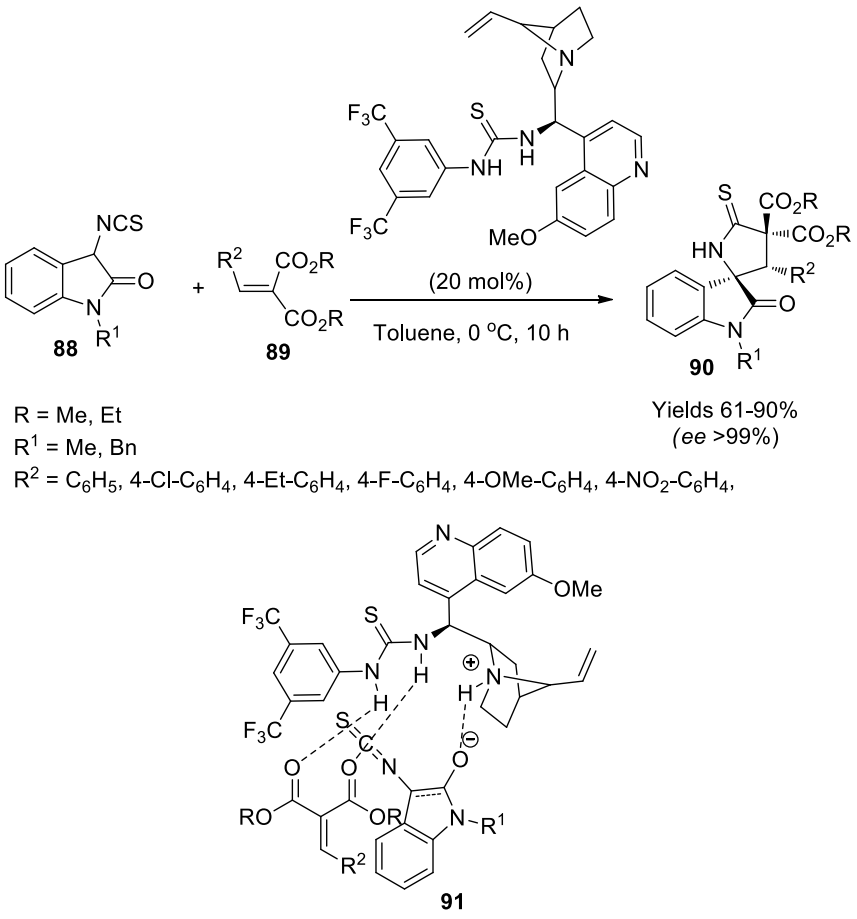


Figure 6.26: Thiourea-based cinchona catalyzed Michael addition reaction.

catalyst under toluene solvent medium. Significant yields (61–90%) of products with superb diastereo- (*dr* up to 99:1) and enantioselectivities (*ee*, >99%) were achieved at 0 °C for 10 h reaction time (Figure 6.26). The addition reaction involved through hydrogen bonding with catalyst thiourea and arylidene, and *si-si* face attack on the arylidene substrate of Micheal addition through a transition state (**91**), which leads to the spiro derivatives.

An asymmetric Michael addition reaction developed in the presence of quinine-based squaramide organocatalyst by Wang and co-workers [75]. The vinylogous Michael reaction was carried out between the unsaturated *γ*-butyrolactam (**92**) and various 2-enoylpyridines (**93**) in a mesitylene solvent medium. The use of 10 mol% of catalysts gave superior results (**94**) with excellent yields (78–99%) and high enantioselectivity (*ee*, >99%) at 40 °C for 26 h reaction time (Figure 6.27). The butyrolactam enolate from *si*-face attacks the enoylpyridine *β*-position through a transition state (**95**), which gives the desired products.

Luo et al. [76], have described the asymmetric Michael addition reaction by applied quinine–thiourea catalyst. The 20 mol% of catalyst performed effectively and gave an

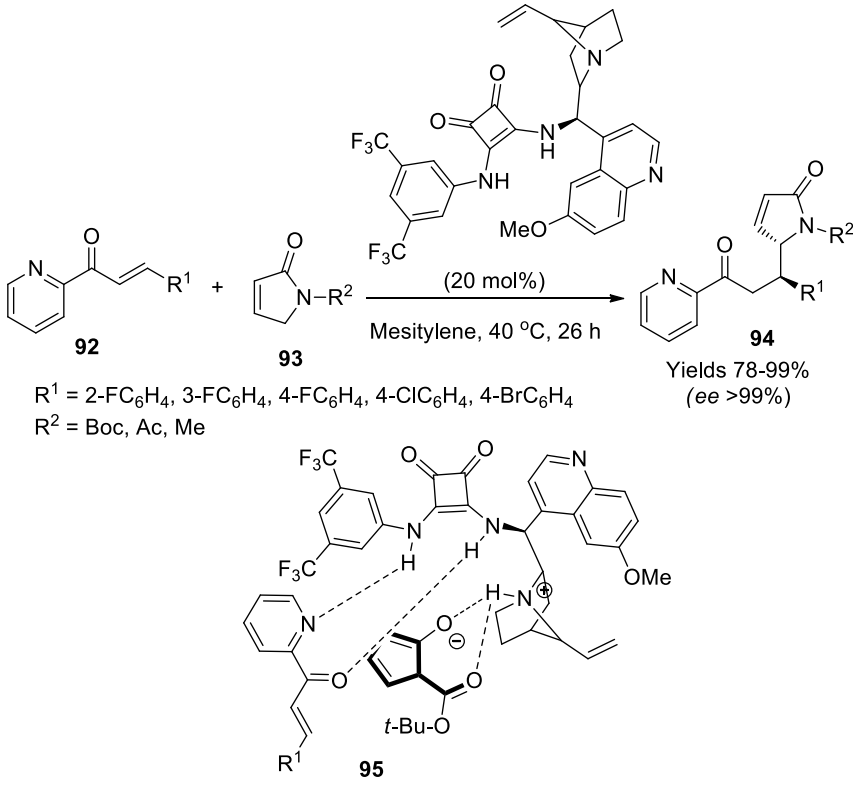


Figure 6.27: Quinine-based squaramide catalyzed Michael addition reaction.

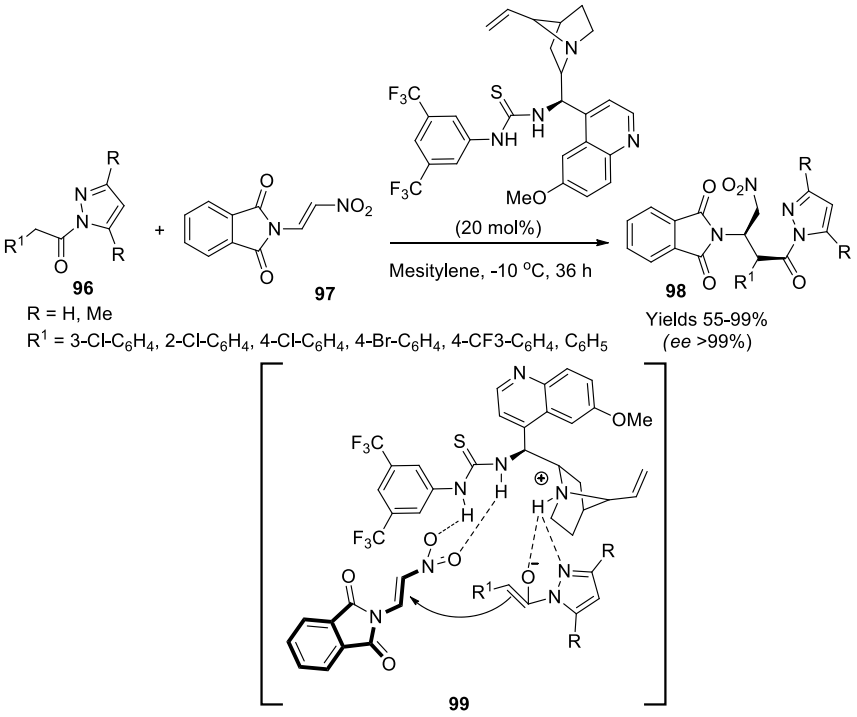


Figure 6.28: Quinine–thiourea catalyzed Michael addition reaction.

excellent yield (55–99%) of *γ*-nitro, *β*-amino amide derivatives (**98**). The addition reaction was conducted between the substituted pyrazoleamide (**96**) and phthalimidonitroethene (**97**) in mesitylene solvent at –10 °C (Figure 6.28). While the unsubstituted pyrazoleamide substrate resulted in the lower yield of the corresponding product when related to the other functional groups' substituted moieties. The protocol offered the high enantio- (*ee*, >99%) and diastereo-selective (*dr* >20:1) derivatives and the reaction involved through the transition state (**99**) with the *Re*-face attack.

6.4 Conclusions

The utilization of small organic compounds as catalysts has developed rapidly, and it has emerged as a dominant synthetic technique complementary to metal-catalyzed organic conversions. The organocatalysis field has enhanced the advancement of innovative approaches to make varied chiral molecules. In recent days, researchers placed enormous effort towards designing and fusing simpler organocatalysts to synthesize enantioselective molecules due to their high effectiveness. The organocatalytic asymmetric aldol and Michael addition reactions are the important powerful

tool to accomplish enantiomerically pure products. These methodologies are often applied to acquire chiral molecules with excellent enantioselectivity and yields. Here we described the organocatalytic aldol and Michael addition reaction for carbon–carbon bond forming reactions with their stereoselectivity. It emphasizes the continuous advances with organocatalysts in asymmetric aldol and Michael reactions, leading to future innovations.

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Gyan Chandra Pariyar and Pranab Ghosh*

7 Enzyme-catalyzed synthesis of bioactive heterocycles

Abstract: Enzymes are proteins that functions as biological catalyst. It is now a known fact that enzyme can catalyze many synthetic operations better than the conventional reagents. Not only in the synthesis of natural products, they can also be applied for construction of varieties of unnatural compounds. In this chapter, Pariyar and Ghosh have discussed in brief synthesis of various biologically active heterocyclic compounds using different enzymes as catalysts. Among various enzymes, laccases, trypsin, α-amylase and Bakers' yeast are few that are easily available and have been extensively explored for various synthetic strategies. This chapter will definitely serve as valuable source of information to the readers in the field of enzyme-catalyzed reactions.

Keywords: biologically active heterocyclic compounds; environment friendly; enzyme-catalyzed; immobilized.

7.1 Introduction

In spite of having a huge number of chemical reagents, chemists do look to exploit enzymes as a catalyst in organic synthesis. The major reason behind this is that there are reports of several synthetic methodologies where enzymes are demonstrated to be superior catalysts as compared to conventional reagents. Enzymes are a protein that catalyzes biochemical reactions and have now evolved to take specific jobs in metabolic and biosynthetic strategies. Enzymes are known to catalyze almost all widespread transformation in organic synthesis such as hydrolysis, oxidation–reduction and condensation reactions. Enzymes are specific with respect to the reaction they catalyze as well as the position on a molecule they attack. Many enzymes are also known to show stereospecificity in addition to regiospecificity and the operations are carried out under mild conditions in aqueous solution at temperatures under 50 °C.

More than 2000 enzymes have been isolated so far and about 50 of them have been successfully affianced for various organic synthesis. Earlier people thought that enzymes are very expensive and are too specific to explore for the use in organic synthesis. However such perception is not valid these days. Many enzymes have shown their ability to be used as catalyst for the synthesis of unnatural product with synthetic

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values [1–3]. Enzyme-catalyzed reactions have now been successfully employed in the synthetic route of chiral synthons. It also have been used to synthesize low molecular weight compounds like sugar and peptides to much complex molecules such as polypeptides, oligosaccharides, nucleotides etc. The field of enzyme catalyst in synthesis has further gained interest due to discovery of catalytically active antibodies [4–7]. Further with growing environment concerns, enzyme-catalyzed organic synthesis has provided an alternative way for robust environmental friendly synthetic procedures.

Enzyme catalytic promiscuity, a process in which the single active site of an enzyme has the ability to catalyze various transformations of non-natural as well as natural substrates [8–12] is also gaining increasing field of interest as more and more catalytic promiscuities in existing enzymes are now been discovered. Investigating enzyme catalytic promiscuity not only helps to gain fundamental knowledge of the enzymes/substrates interactions but also give an insight about better understanding on metabolic pathway during the biosynthesis of secondary metabolites.

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide and covered the largest area of classical organic synthesis. They play important role in processes and industries as well. It is well known that more than 90% of new drugs consist of heterocyclic compounds, which play a vital role as interface between chemistry and biology (Figure 7.1).

Nowadays, methodologies on exploring the synthesis of most profuse and integral scaffold, heterocyclic compounds such as triazole, tetrazole, pyranopyrazole, oxadiazole, thiazole, oxazole, etc. have started gaining focus since they are found in a large number of bioactive natural products, synthetic drugs and pharmaceuticals. Heterocycles have received much attention recently due to its diverse applicability in different fields, such as drugs in pharmaceuticals due to low toxicity and high lipophilicity, in coordination chemistry as ligands as they have the ability of formation of stable complexes with various metal, in catalysis technology, in medicinal chemistry, in photographic industry, in organometallic chemistry as effective stabilizers of metallopeptide structures, in various material science applications and also broadly used as herbicides and fungicides in agricultural industries. Owing to their stability over broad pH range, good tolerance of oxidizing and reducing agent, they are considered as a versatile moiety in organic synthesis. Heterocyclic drugs are explored in pharmaceutical and medicinal industry due to its vast array of activities like antihypertensive, antiallergic, antibiotic and anticonvulsants which are well documented in literature. Beside, in treatment of dreaded diseases such as cancer and AIDS heterocyclic drugs are very effective. Hence chemists are taking keen interest in development of various methodologies for the synthesis of different bioactive heterocyclic molecule and recent synthetic derivatives based on this reaction. A huge library of methodologies has so far been reported for the synthetic pathway of heterocyclic compounds [13–20].

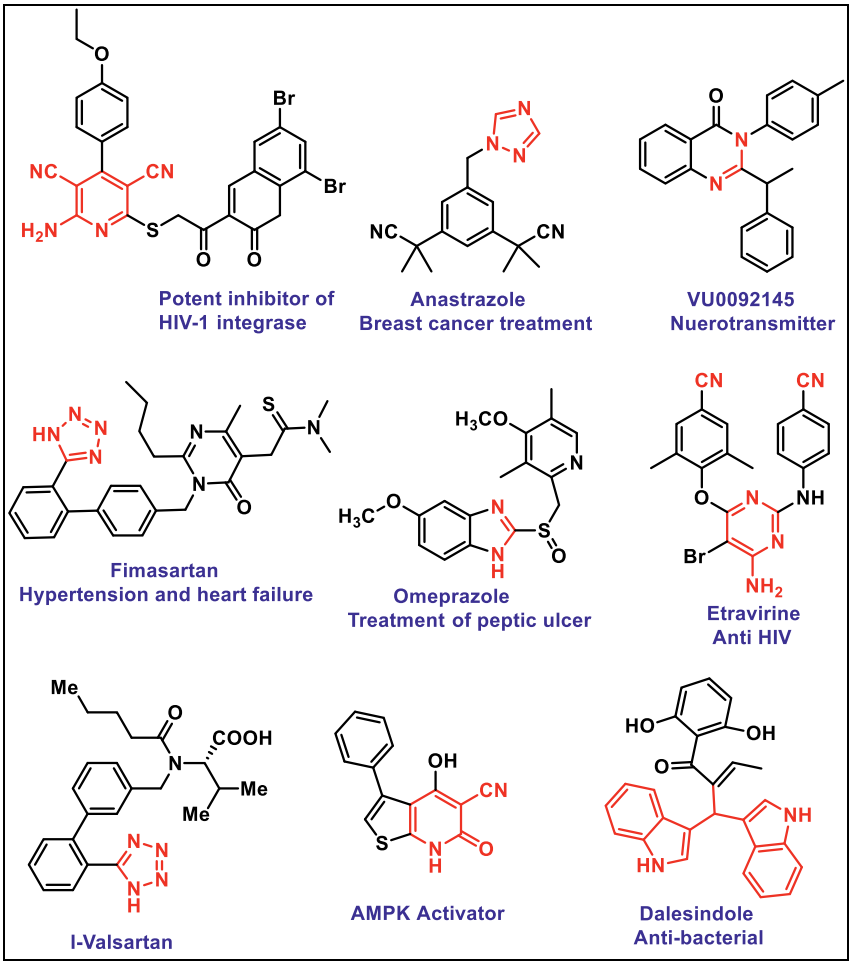
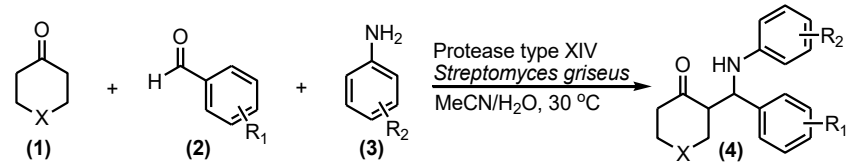


Figure 7.1: Biologically active heterocyclic compounds.

7.2 Protease-catalyzed synthesis of heterocyclic compounds

Protease has been utilized as a catalyst for the synthesis of biologically active heterocyclic compounds and gives good results with high enantioselectivity and distereoselectivity.

Y. Xue et al. in 2012 reported the use of protease type XIV isolated from *Streptomyces griseus* (SGP) to be the unprecedented enzyme-catalyzed asymmetric Mannich reaction (Figure 7.2) [21]. This three-component asymmetric reaction was demonstrated to give enantioselectivity upto 88% as well as diastereoselectivity upto 92%. They



R_1 = H, Cl, Br, F, CH_3, CN, NO_2
R_2 = H, Cl, Br, CH_3, OCH_3
X = CH_2, S

Figure 7.2: SGP-catalysed asymmetric Mannich reaction.

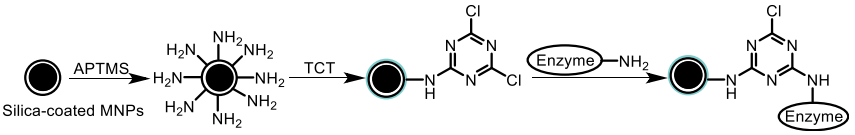


Figure 7.3: Covalent immobilization of enzyme on TCT-modified MNPs.

reported that the specific natural folds present in SGP played the most important factor for the stereoselectivity in this methodology. Other factors including temperature, pH, molar ratio of the reactants, solvent as well as water content were also screened during the course of the reaction. Mentioning the example of enzyme catalytic promiscuity, they further suggested a good scope of SGP-catalysed reactions in the field of enzyme catalyzed methodologies. During their investigation using various substituted aromatic aldehydes, they mentioned that those reactants having electron-withdrawing groups showed more efficiency in enantioselectivity and diastereoselectivity as compared to the aldehydes with electron-donating groups;

7.3 Lipase-catalyzed synthesis of heterocyclic compounds

W. Zhang et al. were successful to covalently immobilize mucor miehei lipase (MML) on 2,4,6-trichloro-1,3,5-triazine (TCT)-modified magnetite nanoparticles [22]. TCT-modified MNPs can be prepared using two-step modification procedure when functionalization on the surface of silica coated MNPs using 3-aminopropyltriethoxy silane (APTMS) for the introduction of amino group is the first step followed by treatment with TCT which results in TCT- modified MNPs. These modified MNPs can then be used as support for immobilization of lipase (Figure 7.3).

The immobilized MML was then used to design a protocol for the preparation of functionalized 4*H*-Chromenes **(7)** (Figure 7.4). Their study revealed that lipase acted as an efficient catalyst for this multi-component reaction as compared to the free MML.

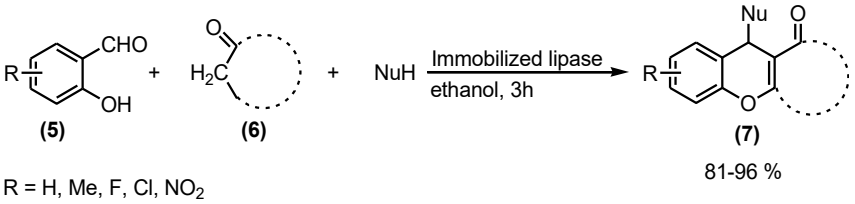


Figure 7.4: Immobilized MML for the synthesis of functionalized 4*H*-chromenes **(7)**.

The possible mechanism may be that the lipase molecule may get dispersed on the surface of the small and nonporous MNPs which might provide good orientation. This may result in high affinity and more sites for the substrates molecules. This synthetic pathway suggested high yield of functionalized 4*H*-chromenes **(7)** under optimal conditions in 3 h. Substrates containing electron-donating groups were reported to give better yield of the product as compare to the electron-withdrawing group. Reusability of the catalyst, short reaction time and environment friendliness were the notable advantages of the protocol.

W. Zhang et al. developed a methodology where lipase obtained from *Mucor miehei* was used as a catalyst for a three-component reaction during the synthesis of indolyl 4*H*-chromenes **(10)** (Figure 7.5) [23]. Good to excellent yield of the products were reported in presence of ionic solvent 1-ethyl-3-methylimidazolium tetrafluoroborate, [EMIM][BF_4] and lipase as a biocatalyst. The reaction was also carried out in presence of solvents like ethanol and water but they only gave moderate yield of the product. Further use of ionic solvent also helped in its reusability as well as that of the catalyst during the reaction. The reaction was temperature dependent and maximum yield of the product was obtained at 60 °C. Presence of electron-withdrawing group on aromatic aldehyde showed lower yield of the product. Environmental friendliness, simple work up procedure, shorter reaction time and excellent yield were some of the advantages of the protocol which helped them in synthesis using a variety of different substrates.

A domino acylation/cyclization procedure for the synthesis of 2-alkybenzimidazole **(13)** was demonstrated by L Wang et al. in 2010 (Figure 7.6). Using immobilized lipase obtained from *Mucor miehei* (MML) as a catalyst, a solvent-free procedure for the reaction

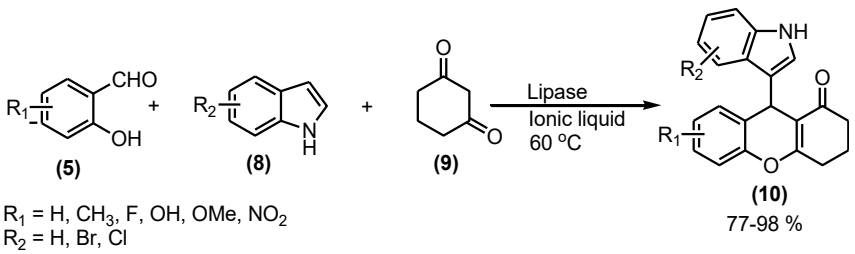


Figure 7.5: Lipase catalyzed synthesis of indolyl 4*H*-chromenes via a three-component reaction.

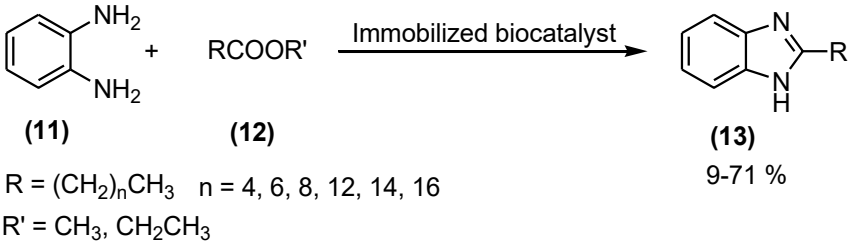


Figure 7.6: Enzyme assisted domino synthesis of 2-alkylbenzimidazoles **(13)** in solvent-free condition.

between *o*-phenylenediamine **(11)** and fatty acid esters **(12)** were reported to be a proficient method for the synthesis of 2-alkylbenzimidazole **(13)** [24]. A vast array of the substrates was screened and a good yield of the products was obtained using this protocol. Reactivity of methyl fatty acid ester **(12)** having moderated chain length was shown to give the best result. A detailed study of the mechanism was also done by them. Hence, this reaction was reported to be an excellent procedure having a vide scope in the synthesis of heterocyclic compounds.

A number of catalyst has been reported so far for the synthesis of bis(indolyl) alkanes **(15)**. For example, H-S Mona was successful in synthesis of bis(indolyl)alkanes **(15)** using TiO_2 [25]. Similarly P. K. Pradhan et al. reported $InCl_3$-NMTA as a catalyst for its synthesis [26]. However these methodologies bring drawbacks such as use of heavy metals, tedious work-up conditions etc. Z. Xiang et al. successfully removed these drawbacks and used for the first time lipase obtained from porcine pancreas Type II (PPL) as a catalyst for the synthesis of bis(indolyl)alkanes **(15)** by cascade reaction procedure (Figure 7.7) [27]. By reacting indole **(14)** with aldehydes **(2)**, moderate to excellent yield of bis(indolyl)alkanes **(15)** can be seen from their procedure. It was also reported that instead of pure solvents, a mixed solvent of water and 1,4-dioxane could enhance the substrate stability and improve coexistence of the substrates which eventually was responsible for the better yield of the product when the reaction was carried out at 50 °C. Presence of electron-withdrawing group on benzene ring was reported to improve the yield of the product as compared to the electron-donating group.

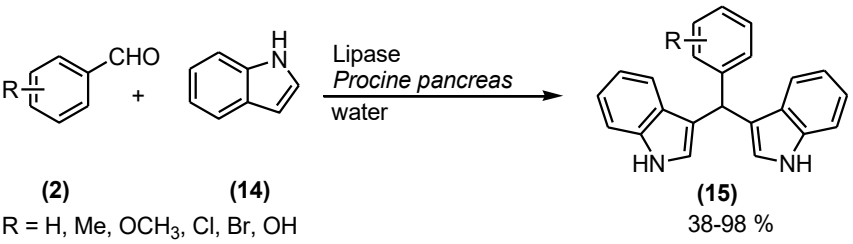


Figure 7.7: Procine pancreas lipase (PPL)-catalyzed synthesis of bis(indolyl)alkanes **(15)**.

J.-C. Xu et al. established the use of lipase derived from *Porcine pancreas* (PPL) as a biocatalyst for the synthesis of tetrahydrochromene derivatives **(18)** by the reaction between benzaldehyde **(2)**, malononitrile **(16)** and cyclohexane-1,3-dione **(17)** (Figure 7.8) [28]. This green one-pot synthetic methodology was reported to be an efficient procedure for the synthesis of tetrahydrochromene derivatives **(18)** in presence of water as a solvent. Under room temperature a vast array of substrates were screen and it was found that PPL acted as good catalyst giving good to excellent yield of the products. Various aromatic and aliphatic aldehydes were investigated and they found that all substrate gave good yield of the product. However as evident from their publication, the reaction of cyanoacetic ester gave lower yield as compared to malonitrile **(16)**.

F Yang et al. published a simple reaction procedure for the synthesis of benzo[*g*] chromene derivatives **(20)** (Figure 7.9) [29]. Lipase was used as the biocatalyst for the reaction protocol. The reaction was reported to be efficient and high yield of the products were obtained using the methodology. Aromatic aldehydes **(2)** with electron-withdrawing or electron-donating groups were noted to give satisfactory yield of the product. Comparing with the earlier reported methods, they further predicted that not only the reaction methodology was environmentally friendly, atom economic and simple, but their work enhanced the utility of lipase as a catalyst in organic synthesis. Immobilization is supposed to be an important tool which can avoid aggregation of enzyme in organic solvents and hence can help in recovery and reuse of catalyst with losing its activity.

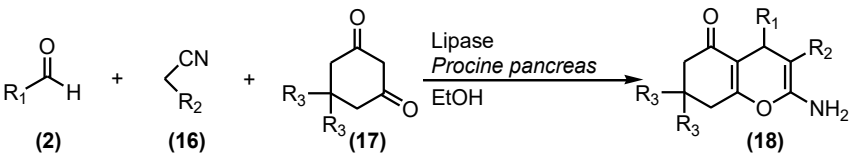


Figure 7.8: One-pot three-component synthesis of tetrahydrochromene derivatives **(18)** catalyzed by lipase.

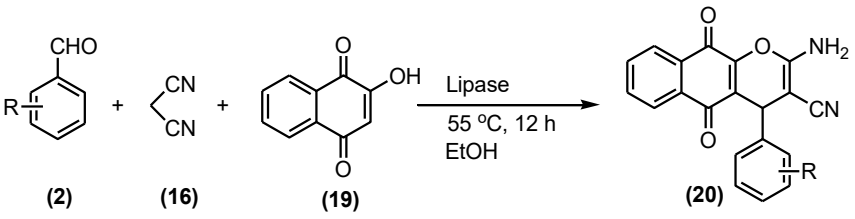


Figure 7.9: One-pot three-component synthesis of benzo[*g*]chromene derivatives **(20)** assisted by lipase.

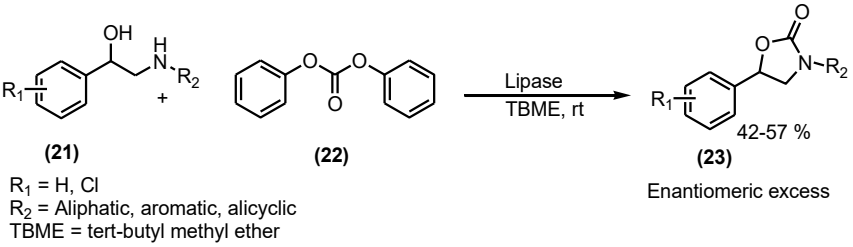


Figure 7.10: Lipase catalyzed synthesis of chiral oxazolidinone derivatives **(23)**.

In 2015, Y. Zhang et al. published lipase-catalysed synthesis of enantioenriched oxazolidinone derivatives **(23)** (Figure 7.10) [30]. Using carbonate donors and lipase catalyst they were able to synthesize oxazolidinone derivatives **(23)** in moderate to good yield. The mechanism was proposed to be a two-step process where following the initial carbamation step, cyclization with the help of lipase as catalyst was reported to give high enantiopurities. Here the carbonates were used as double acyl donors. Adding chloro-substitution to phenyl did not showed and effect in the yield of the product. However increase in size of the amine substituent gave lower yield of the product.

D. Yadav et al. used a number of immobilized lipases for the synthesis of oxazolidin-2-one **(27)** by the reaction between 2-aminoalochol **(24)** and dimethyl carbonate **(25)** [31]. However they found that the best result was obtained with *Candida antarctica* lipase B (Novozyme 435) (Figure 7.10). They published that the reaction followed two step mechanisms. In the first step, methyethyl (2-hydroxyethyl) carbamate **(26)** was formed as an intermediate when 2-aminoalochol **(24)** reacted with dimethyl carbonate **(25)** in presence of Novozyme 435. The intermediate again in presence of the same biocatalyst undergoes further reaction to eventually give the final product 3-ethyl-1,3-oxazolidin-2-one **(27)** (Figure 7.11). Different parameters that were responsible for affecting the rate of reactions and conversion in both the steps which included agitation speed, catalyst loading and solvent and reaction temperature were thoroughly studied. They also proposed the probable mechanism where methanol was generated as a co-product with the formation of the intermediate methyl ethyl (2-hydroxyethyl) carbamate which after rearrangement gave the final product. They also studied the reaction kinetics and kinetic constants and activation energy for the reaction were

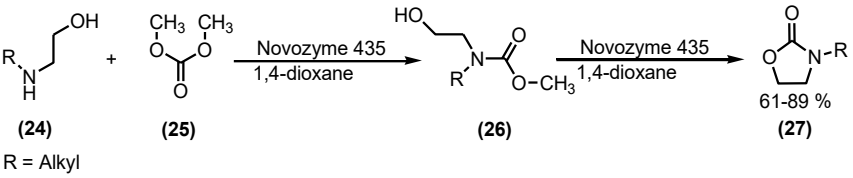


Figure 7.11: Immobilized enzymatic synthesis of 3-ethyl-1,3-oxazolidin-2-one **(27)**.

determined. The reaction was reported to be first of its kind where consecutive enzyme catalyzed process was studied. Further it was reported that excellent results were obtained by using different 2-aminoalcohols **(24)**.

7.4 Pepsin-catalyzed synthesis of heterocyclic compounds

M.-J. Zhang et al. published a methodology where pepsin was used as a catalyst for the synthesis of γ,γ-disubstituted butenolides **(30)** (Figure 7.12) [32]. A Micheal type addition reaction between maleimides **(29)** and deconjugated butenolides **(28)** was demonstrated in presence of water where good to excellent yield of the product was reported. The pepsin used by them as the catalyst was obtained from porcine gastric mucous.

7.5 Amylase-catalyzed synthesis of heterocyclic compounds

H. Zheng et al. have developed a protocol where *α*-amylase obtained from hog pancreas was used as a catalyst for the synthesis of substituted pyrroles **(33)** (Figure 7.13) [33]. During this Paal–Knorr reaction, a vast array of substrates was used for the synthesis of different *N*-substituted pyrrole derivatives **(33)** where good to excellent yield of the product were reported by them. They showed that primary amine with electron-withdrawing group or electron-donating group gave good yield of the product. High efficiency of the catalyst, mild reaction conditions and environment friendliness were some of the advantages of the protocol as published by them. Although the detail catalyst mechanism was not established by them, but the protocol was described to be an advantageous tool for the synthesis of various pyrrole derivatives **(33)**.

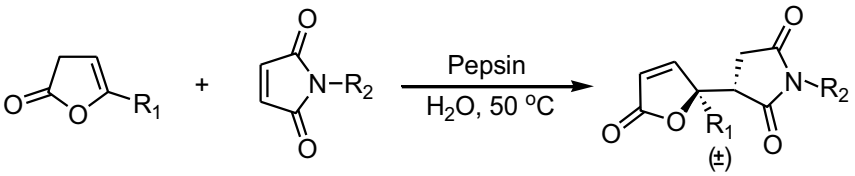


Figure 7.12: Pepsin catalyzed Michael addition of deconjugated butenolides **(28)** and maleimides **(29)** in water.

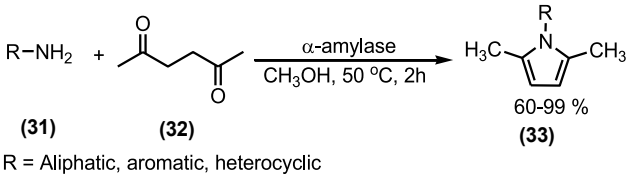


Figure 7.13: α-Amylase catalyzed synthesis of *N*-substituted pyrrole **(33)** derivatives.

S. Dutt et al. were successful to demonstrate the application of α-amylase in the synthesis of 3-acetyl quinolone **(38)** (Figure 7.14) [34]. Using 2-amino benzaldehyde **(34)** and methyl vinyl ketone **(35)** in a cascade reaction which consisted of aza-Michael addition/aldol condensation, the desired product was isolated by them at 40 °C. However the yield of the product was reported to be low and they suggested further investigation in order to improve the yield of the product.

7.6 Bakers' yeast catalyzed synthesis of heterocyclic compounds

U. R. Pratap et al. reported a methodology where Bakers' yeast was employed as a catalyst for the synthesis of 2-substituted benzothiazoles **(40)** (Figure 7.15) [35]. In their process, condensation between aldehydes **(2)** and 2-aminothiophenol **(39)** was carried out in DCM which furnished moderate to good yield of the products in presence of Bakers' yeast. Bakers' yeast promises an excellent source of extracellular enzymes. They proposed that these enzymes may be responsible for the acceleration of cyclocondensation between aldehydes **(2)** and 2-aminothiophenol **(39)** which may be due to the formation of enzyme-

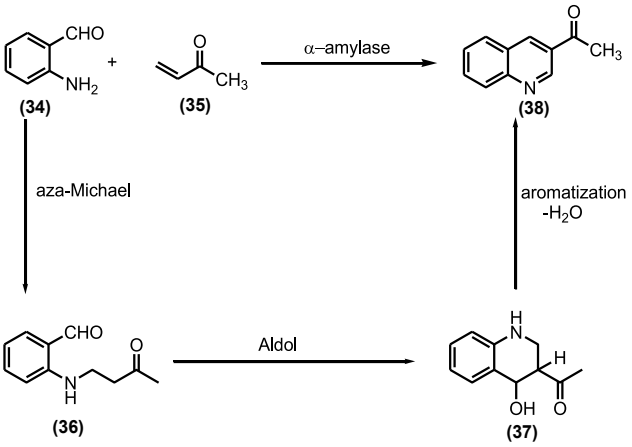


Figure 7.14: α-Amylase catalyzed synthesis of 3-acetyl quinoline **(38)**.

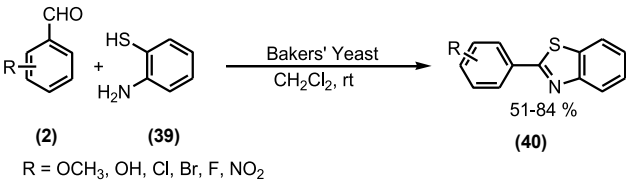


Figure 7.15: Bakers' yeast catalyzed synthesis of benzothiazoles **(40)**.

2-aminothiophenol non-covalent complex or it may be due to the formation of enzyme-aldehyde complex. No significant effect of electron-withdrawing or electron-donating groups present on aldehydes was reported on the yield of the reaction. The same reaction may also be possible if lipase is used as a catalyst.

7.7 Acylase-catalyzed synthesis of heterocyclic compounds

Z.-Q. Liu et al. put forward a methodology where Acylase "Amano" (AA) was utilised as a catalyst for the synthesis of pyridin-2-ones **(43)** (Figure 7.16) [36]. This was a one-pot reaction strategy where cyanoacetamide **(41)**, aldehydes **(2)** and ethyl acetoacetate **(42)** or cyclohexyl acetoacetate **(42)** underwent Knoevenagel condensation, Michael addition, intramolecular cyclization and oxidization reaction to give the final product. A number of different types of substrates were used by them in order to synthesize aromatic, aliphatic and hetero-aromatic pyridin-2-ones **(43)** in good yield. Solvent was reported to have played a pivotal role in this transformation as they influenced catalytic activity of the enzyme used. Various solvent were screened during the course of this methodology and it was finally established that best results was obtained when the reaction was carried out in ethylene glycol. Electron-withdrawing group on aromatic ring were reported to furnish better yield of the product as compared to electron-donating group.

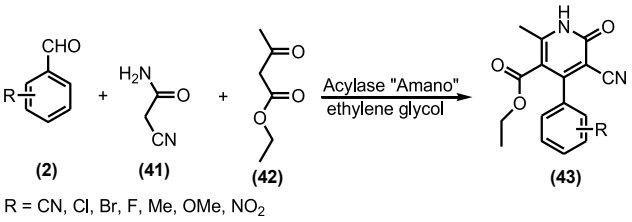


Figure 7.16: Three-component domino synthesis of pyridin-2-ones **(43)**.

7.8 Trypsin-catalyzed synthesis of heterocyclic compounds

Y. Yu et al. published an eco-friendly strategy as compared to traditional chemo-catalysed reaction by using enzymes as catalyst for the synthesis of 4*H*-pyrimido[2,1-*b*] benzothiazole derivatives **(46)** (Figure 7.17) [37]. In this methodology, trypsin was used as a multi-functional catalyst and vinyl acetate played the role of *in situ* aldehyde generator. Here ethylene glycol had a dual character for being not only the solvent but was also responsible during trans esterification with vinyl acetate and hence provided continuous supply of aldehydes **(2)**. The probable mechanism was proposed where they argued that the reaction actually consists of two independent procedures and both of these were catalysed by trypsin. The first process was responsible for continuous supply of the substrates required for the second reaction and hence was effective in reducing the loss of aldehydes **(2)** due to volatilization, polymerization and oxidation of aldehyde which eventually reduced the negative effect due to excess aldehydes **(2)** on the catalyst. One-pot Beginelli three-component reaction between β-ketoesters **(44)**, aldehydes **(2)** and 2-amino benzothiazole **(45)** and catalysed by trypsin was thus used for the synthesis of various benzothiazole **(46)** derivatives in good yield. With electron-withdrawing group on the aromatic aldehyde, the yield of the product was much higher than those containing electron donors.

7.9 Laccase-catalyzed synthesis of heterocyclic compounds

A. Rahimi et al. reported the strategy where laccase obtained from *Trametes versicolor* was used as a biocatalyst for the synthesis of arylsulfonyl-1,2,4-triazolidine-3,5-dione

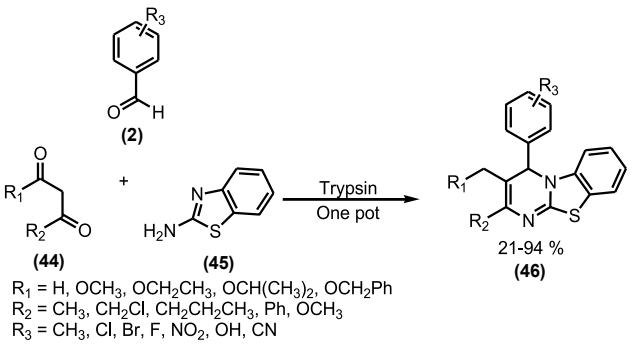


Figure 7.17: Enzyme-catalysed one-pot synthesis of 4*H*-pyrimido[2,1-*b*] benzothiazoles **(46)**.

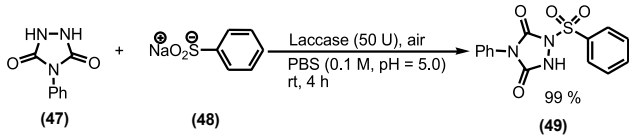


Figure 7.18: Laccase catalyzed synthesis of arylsulfonyl triazolidinediones **(49)**.

derivatives **(49)** (Figure 7.18) [38]. Aerobic oxidation of 4-substituted urazoles **(47)** followed by cross-coupling with sodium benzenesulfinates **(48)** was the mechanism behind the formation of the products. During this process, air was utilized as the oxidant and phosphate buffer solution (PBS), an environmental friendly solvent to give good to high yield of the product.

M. D. Cannatelli et al. proposed an eco-friendly methodology for the synthesis of 2,3- ethylenedithio-1,4-quinones **(52)** (Figure 7.19) [39]. Here, laccases was used as the biocatalyst where its oxidising ability was used to produce *in situ* 1,4-quinones **(51)**. The 1,4-quinones **(51)** thus formed underwent nucleophilic addition with 1,2-ethanedithiol and subsequently followed by oxidation and addition to afford the desired products in good yield. Water was used as the solvent in the reaction. Stability of 1,4-quinone **(51)** generated *in situ* played a pivotal role in determination of whether cross coupling reaction would occur. Small cyclic sulphur compounds were also detected in this reaction which may have been formed due to competing radical reactions. Though research has suggested that small thiols inhibit laccases, this study established the fact that additions related to small thiols catalysed by laccases are feasible.

V Hahn et al. published laccases catalysed strategy in which first oxidative C–N bond is formed and then it was followed by cyclization involving dihydroxybenzoic acid derivatives along with heteroaromatic amines. Laccases obtained from *Myceliophthora thermophila* and *Pycnoporus cinnabarinus* was used as a catalyst (Figure 7.20)

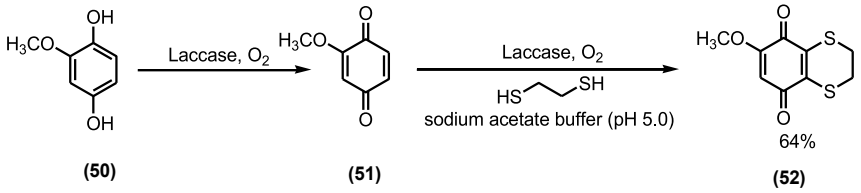


Figure 7.19: Synthesis of 2,3-ethylenedithio-1,4-quinones **(52)** using laccase as a catalyst.

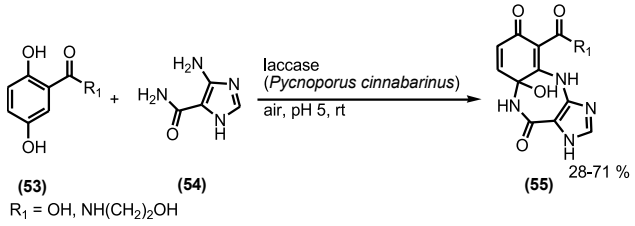


Figure 7.20: Enzymatic cyclizations using laccases.

[40]. Cyclization involving 2,5-dihydroxybenzoic acid derivatives **(53)**with five membered ring amines **(54)** in air as oxidant led to the synthesis of cycloheptenes **(55)** in good yields.

H. T. Abdel-Mohsen et al. described synthesis of pyridines by oxidation of 1,4-dihydropyridines **(57)** catalysed by laccases (Figure 7.21) [41]. The biocatalyst in presence of air as oxidant gave good yield of the desired product.

S. Hajdok et al. reported an efficient methodology involving domino reaction between catechols **(59)** and cyclohexane-1,3-diones **(58)** for the synthesis of 3,4-dihydro-7,8-dihydroxy-2*H*-dibenzofuran-1-ones **(60)** (Figure 7.22) [42]. Laccases obtained from *Agaricus bisporus* was used as biocatalyst and air was used as an oxidant in this methodology. Among the various advantages of the reactions, high yield of the product, mild reaction condition and environment friendliness were some of them. Phosphate buffer was used to maintain the pH at 5.96 and the reaction was carried out at room temperature.

S. Hajdok et al. employed laccases as a biocatalyst for the synthesis of various types of annulated benzofurans **(62)** by reaction between heterocyclic 1,3-dicarbonyls (pyridinones, quinolinones, thiocoumarins) **(61)** and catechols **(59)** (Figure 7.23) [43]. The reaction was performed under mild conditions using aerial oxygen as the oxidant giving moderate to good yield of the product. When the reaction was carried out with barbituric acid derivatives, formation of dispiropyrimidinone derivatives exclusively was observed. The structures of all the products were established using NMR spectroscopy and X-ray crystallography.

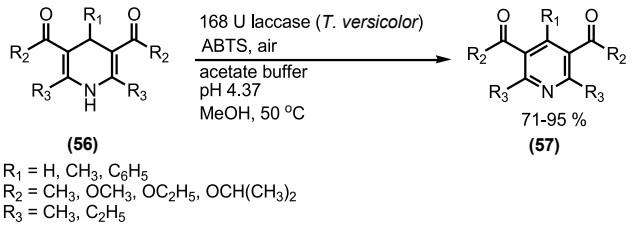


Figure 7.21: Laccase assisted oxidation of Hantzsch 1,4-dihydropyridines **(57)** to pyridines.

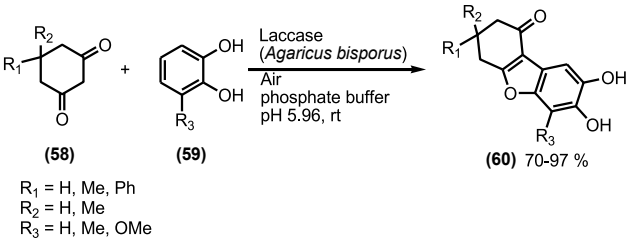


Figure 7.22: Laccase catalysed synthesis of 3,4-dihydro-7,8-dihydroxy-2*H*-dibenzofuran-1-ones **(60)**.

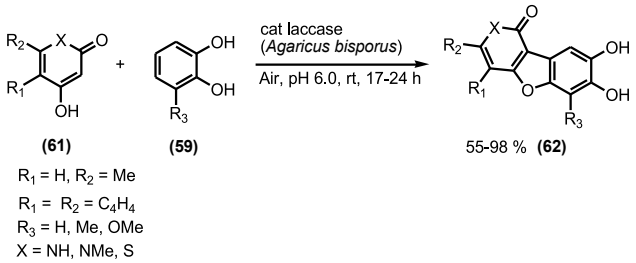


Figure 7.23: Laccase assisted domino reaction between catechols **(59)** and heterocyclic 1,3-dicarbonyls **(61)**.

C. Ganachaud et al. reported use of laccases as an excellent catalyst that brought about trimerization of indole **(63)** for the synthesis of 2,2-bis(3′-indolyl)-indoxyl **(64)** (Figure 7.24) [44]. The identification of the compound was established by them using X-ray diffraction technology. Optimization of the reaction condition was done and it was found that the use of dioxygen overpressure and TEMPO as a solvent gave the yield by more than 50% of the desired product. 2,2-Bis(3′-indolyl)-indoxyl **(64)** is a natural product that can be isolated from bacterial sources and this methodology provides a pathway for biosynthesis of the product. In order to account for the role of laccases as catalyst, a possible mechanism involving initial formation of transient indole hydroperoxide was established.

H. Leutbecher et al. proposed the synthesis of 2-aryl-1*H*-benzimidazoles **(13)** by the reaction involving benzaldehydes **(2)** and *o*-phenylenediamine **(11)** (Figure 7.25) [45]. The

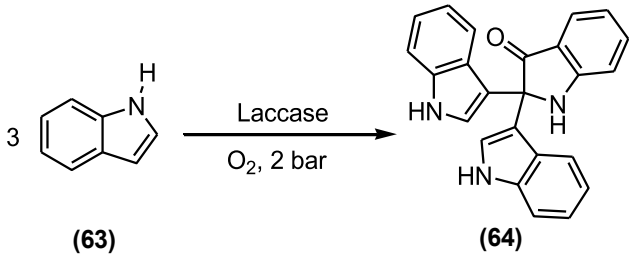


Figure 7.24: Trimerisation of indole **(63)** mediated by laccase.

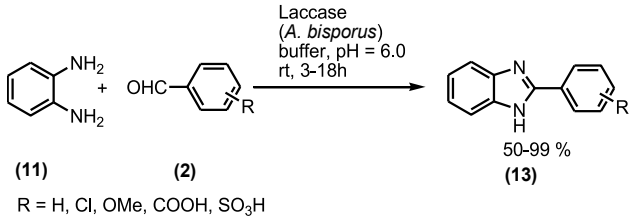


Figure 7.25: Laccase mediated synthesis of 2-aryl-1*H*-benzimidazoles **(13)**.

reaction was catalysed by laccases obtained from *A. bisporus*. The reaction involves aerobic oxidation of one of the C–N bond of the amine to form a C–N double bond. It was further established that this laccases catalysed methodology was far more superior to non-enzymatic reactions in terms of yield and purity of the desired products. They reported that laccase-catalyzed reaction showed better selectivity and also furnished better yield of the product as compared to the reactions in absence of any catalyst.

M. Maphupha et al. successfully used laccases for the synthesis of 2-aryl-1*H*-benzimidazoles **(65)** (Figure 7.26) [46]. Laccases are now established to be valuable oxidizing catalyst and are now widely used for synthesis of pharmaceutically important products. Readily available commercial laccases was thus used by them for this method and have reported to have achieved moderate to good yield of the product. They also reported that chemoselectivity of the product was obtained by using Novoprime Base 268 in acetate buffer and using acetonitrile as a solvent when formation of 3,4-disubstituted benzimidazole was not detected. They reported that solvent had profound effect on the chemoselectivity of the product. With methanol or ethanol as a solvent, formation of undesired *N*-benzylated product **(66)** was also obtained. However, by using DMF or acetonitrile, they were able to minimize the amount of formation of *N*-benzylated product **(66)**. Finally, by using laccase as a catalyst, the chemoselectivity was increased to a great amount as reported by them. Mild conditions, simple work-up process and environment friendly protocol were some of the advantages of this methodology as reported by them. Along with synthesis of various benzothiazole derivatives in good yield.

M. D. Cannatelli et al. used laccases as a biocatalyst for the synthesis of phenothiazones **(68)** (Figure 7.27) [47]. They established direct coupling 2-aminothiophenol

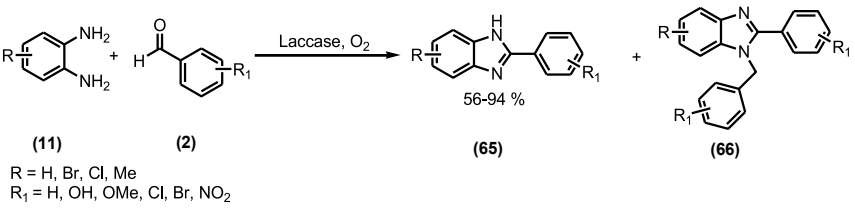


Figure 7.26: Laccase-catalysed route for the synthesis of 2-arylbenzimidazoles **(65)**.

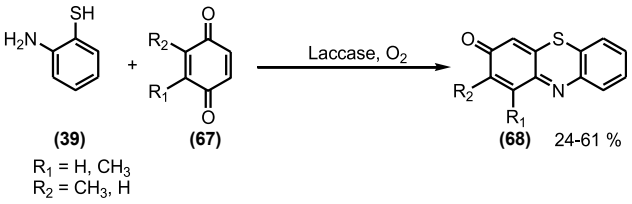


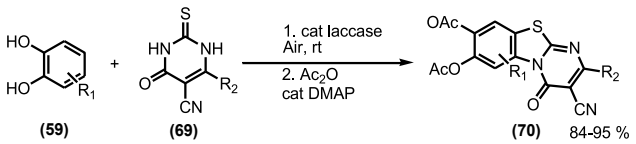
Figure 7.27: Laccase catalysed synthesis of phenothiazones **(68)**.

(39) and 1,4-quinones **(67)** using an aqueous medium can increase the yield of the product significantly in presence of laccases as a catalyst rather than in absence of laccases or *in situ* generation of 1,4-quinones by laccase oxidation of hydroquinone. Different reactivity of aliphatic and aromatic amines towards 1,4-naphthoquinone was also studied by them.

H. T. Abdel-Mohsen et al. published a laccase catalyzed protocol describing domino reaction strategy between 6-substituted-1,2,3,4-tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles **(69)** and catechols **(59)** for the synthesis of pyrimidobenzothiazole derivatives **(70)** (Figure 7.28) [48]. Use of aerial oxygen as oxidant will initiate the course of this reaction. Using mild reaction conditions, this methodology can be utilized for the synthesis of pyrimidobenzothiazoles **(70)** with good yield. Structure of catechols **(59)** and the substituents present in 6-substituted-1,2,3,4-tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles **(69)** controls the regioselectivity of the process. Total structure determination of regioisomeric ring-proton deficient pyrimidobenzothiazoles **(70)** was established based on $^{1}H–^{15}N$ HMBC NMR correlations at natural abundance and experimental $^{1}H–^{13}C$ long-range coupling constants.

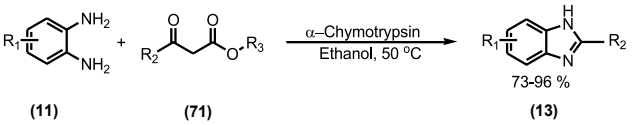
7.10 Chymotrypsin-catalyzed synthesis of heterocyclic compounds

α-Chymotrypsin which belongs to the serine proteases family is a polypeptide known to consist of 245 amino acids. L-S Liu et al. has described the synthesis of 2-substituted benzimidazoles **(13)** from β-ketoesters **(71)** and o-phenylenediamines **(11)** where the reaction was catalysed by α-chymotrypsin (Figure 7.29) [49]. This enzyme-catalyzed reaction was reported to be and efficient methodology for the synthesis of diverse array of benzimidazole derivatives **(13)**. All the substituent was reported to have given good result of the product. Eco-friendliness, mild reaction conditions and high functional group tolerance were some of the advantages as reported by them.



R_1 = H, CH_3
R_2 = C_6H_5, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4
C_2H_5, C_3H_7, $CH(CH_3)_2$

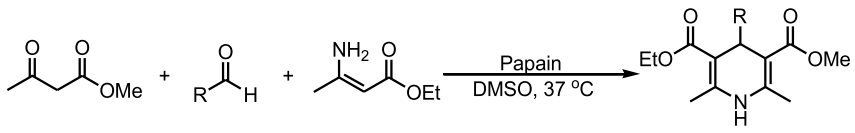
Figure 7.28: Laccase-catalyzed domino reaction for the synthesis of pyrimidobenzothiazole derivatives **(70)**.



(11) (71) (13)

R_1 = H, CH_3, F, Cl, CF_3, NO_2
R_2 = CH_3, CH_2CH_3
R_3 = CH_2CH_3

Figure 7.29: α-Chymotrypsin-catalyzed synthesis of 2-substituted benzimidazole **(13)**.



(71) (2) (72) (73)

R = Aromatic, heterocyclic

Figure 7.30: Papain-catalyzed one-pot synthesis of 1,4-dihydropyridine **(73)**.

7.11 Papain-catalyzed synthesis of heterocyclic compounds

J. Ling et al. were successful in demonstrating the application of enzymatic promiscuity for the synthesis in pharmaceutical industries. 1,4-dihydropyridine **(73)** derivatives has been successfully used as antihypertensive drugs. The authors published a methodology where aldehydes **(2)**, methyl acetoacetate **(71)** and ethyl 3-aminocrotonate **(72)** underwent a one-pot three component reactions for the synthesis of 1,4-dihydropyridine derivatives (Figure 7.30) [50]. The reaction was catalyzed by papain where mild reaction conditions and environment friendliness were the features of the reaction. Aldehydes **(2)** having either electron-withdrawing or electron-donating effects gave moderate to good yield of the product as reported by them. They also found that when the electron-donating substituents were present in the *meta*-position, better results were obtained than their *ortho*- or *para*-substituted analogues.

7.12 Conclusions

In summary, we observed that heterocyclic compounds have been extensively used as biologically active compounds. Majority of drugs that are in use today contains heterocyclic moiety. Heterocyclic drugs are explored due to its vast array of activities like antihypertensive, antiallergic, antibiotic and anticonvulsants which are well documented in literature. A vast number of methodologies have been developed for the

construction of heterocyclic compounds. In summary enzyme-catalyzed reactions are also used extensively in the synthesis of heterocyclic compounds. Different enzymes such as protease, lipase, laccase, pepsin, amylase, Bakers' yeast, acylase, trypsin, chymotrypsin and papain have been identified for such synthesis. With advantages like mild reaction conditions, water as solvents, low temperature and environmental friendliness, enzyme catalyzed protocols are likely to remain a field of interest among chemists for the construction of biologically active heterocyclic moiety. Further, chiral compounds can also be formed in this condition with good enantioselectivity.

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8 Sulfonated β-cyclodextrins: efficient supramolecular organocatalysts for diverse organic transformations

Abstract: The present review summarizes various organic transformations carried out by using sulfonated β-cyclodextrins such as β-cyclodextrin sulfonic acid, β-cyclodextrin propyl sulfonic acid, and β-cyclodextrin butyl sulfonic acid as an efficient, supramolecular reusable catalyst under diverse reaction conditions.

Keywords: β-cyclodextrin sulfonic acid; organic transformations; organocatalysis; sulfonated β-cyclodextrin; sustainable synthesis.

8.1 Introduction

Metal-free organocatalysis is becoming an important tool to carry out diverse organic transformations under environmentally benign conditions because of its ecofriendly, inexpensive, nontoxic nature [1–8]. Among many others, β-cyclodextrin (β-CD) has received significant attention as a supramolecular catalyst [9]. β-CD is a cyclic heptamer composed of seven glucose moieties. It has the ability to form inclusion compounds with different molecules and can bind organic molecules in the hydrophobic pocket [10]. Along with this, the presence of hydroxyl groups at the exterior part provides the polar environment which makes this as an attractive catalyst [11]. Because of the supramolecular inclusion properties, CD was used to prepare some superamphiphiles [12, 13]. It can catalyze chemical reactions by forming reversible host-guest complexes using non-covalent interactions [14, 15]. A large number of methods have been developed by using β-CD as catalyst for diverse organic transformations [16–23]. By using β-CD as catalyst many reactions were carried out even in aqueous medium [24–29]. In-spite of so many advantages, due to its mildness, this supramolecular catalyst failed to catalyze the reactions where a strong catalyst is required. Moreover poor solubility is another drawback of β-CD. Therefore scientists are trying to modify or derivatized this fascinating catalyst to expand its applicability for

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diverse organic transformations [30–32]. Recent studies revealed that in aqueous medium sulfobutylether-β-CD can be used as a solubility enhancer of Remdesivir, a potent antiviral drug and found effective against COVID-19 as well [33]. Under this direction, inclusion of β-CD sulfonic acid (β-CD-SO_3H) as catalyst helps a lot to achieve the goal. Solubility of sulfonated β-CD is much higher in aqueous medium than the β-CD. In 2011, Asghari et al. [34] first synthesized β-CD-SO_3H *via* the sulfonation of one of the hydroxyl groups of the CD ring. Incorporation of the sulfonic acid group enhances the solubility in water compared to the β-CD. Other sulfonated β-CDs such as β-CD propyl sulfonic acid, β-CD butyl sulfonic acid are also showed superior catalytic activity than β-CD.

This review summarizes all the recent organic transformations carried out by using sulfonated β-CD as catalyst under diverse reaction conditions.

8.2 Preparation of sulfonated β-CD

Asghari et al. [34] prepared β-CD-SO_3H by the sulfonation of β-CD using chlorosulfonic acid. They first dissolved β-CD (5.00 g, 4.5 mmol) in 20 mL chloroform and stirred this mixture vigorously. In this mixture they added chlorosulfonic acid (1.00 g, 9 mmol) drop-by-drop at 0 °C. The addition was continued very slowly by taking time upto 2 h under stirring conditions. After completion of the addition, the reaction mixture was further stirred for 2 h to remove generated hydrochloric acid from reaction vessel. Then, they filtered the mixture and washed with methanol. The obtained white residue was dried at room temperature which afforded the corresponding β-CD-SO_3H in the powder form (5.28 g) (Figure 8.1). By titration method they estimated the $-SO_3H$ content and found 0.52 mequiv./g which confirms the monosulfonation of the β-CD.

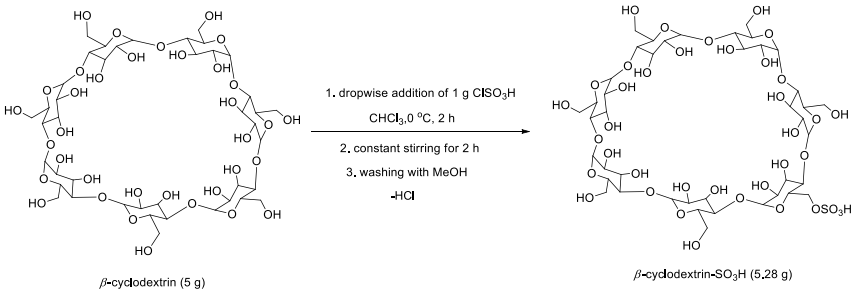


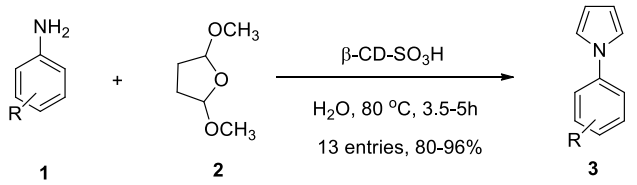
Figure 8.1: Preparation of β-CD-SO_3H from β-CD.

8.3 β-CD-SO_3H catalyzed synthesis of heterocyclic scaffolds

8.3.1 β-CD-SO_3H catalyzed synthesis of *N*-heterocycles

8.3.1.1 Synthesis of pyrrole derivatives

Pyrrole and its derivatives are found to possess significant biological efficacies including antiviral, antibacterial, antiinflammatory, antitumoral, anticancer, and antioxidant activities [35–38]. Because of this biological importance a huge number of methods have been reported for the synthesis of various pyrrole derivatives. For the synthesis of pyrroles, Paal–Knorr [39] and Clauson–Kaas [40] reactions are the widely used protocols. A number of catalysts were used for these reactions which include $Bi(NO_3)_3$ [41], $CeCl_3$ [42], $FeCl_3{\cdot}7H_2O$ [43], Al_2O_3 [44], $Yb(OTf)_3$ [45], $InCl_3$ [46], $Ti(O^iPr)_4$ [47], $RuCl_3$ [48], $CuCl_2$ [49], $CoCl_2$ [50], etc. Though these reported protocols have certain merits still they suffer from a number of demerits such as use of toxic metal catalysts, hazardous solvents, expensive reagents, harsh reaction conditions, costly catalysts, longer reaction time, nonreusability of the catalysts, tedious work up procedure etc. In 2018, Patil and Kumar [51] developed a mild and efficient protocol for the synthesis a series of pyrrole derivatives using β-CD-SO_3H as an efficient reusable metal-free organocatalyst. A series of 1-aryl-pyrrole derivatives (**3**) was synthesized *via* Paal–Knorr reaction strategy between substituted anilines (**1**) and 2,5-dimethoxytetrahydrofuran (**2**) using β-CD-SO_3H as catalyst in water at 80 °C (Figure 8.2). A plausible mechanism of this conversation is depicted in Figure 8.3. When the others conditions remain unchanged, the same reaction using β-CD as catalyst afforded only 20% of the desired product even after 24 h. The same scaffolds were also synthesized *via* Clauson–Kaas reaction starting from substituted anilines (**1**) and hexane-2,5-dione (**4**) in the presence of a catalytic amount of β-CD-SO_3H under solvent-free conditions at ambient temperature (Figure 8.4). The catalyst here was found to play a dual role. It behaves like a phase transfer reagent as well as an acidic catalyst. It is noteworthy to mention that for both the cases the catalyst was recycled for five successive runs without any loss in its catalytic efficiency.



R = H, 4-OCH_3, 4-CH_3, 2-CH_3, 2-I, 4-Cl, 4-Br, 3-CF_3, 4-NO_2, 4-Ph

Figure 8.2: β-CD-SO_3H catalyzed pyrrole synthesis *via* Clauson–Kaas reaction.

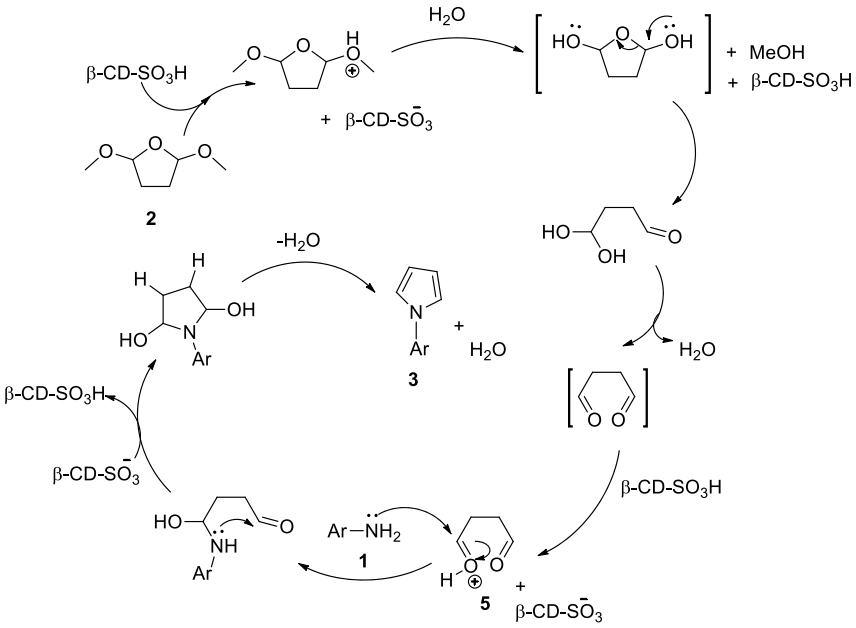


Figure 8.3: Plausible mechanism of β-cyclodextrin sulfonic acid catalyzed synthesis of pyrroles.

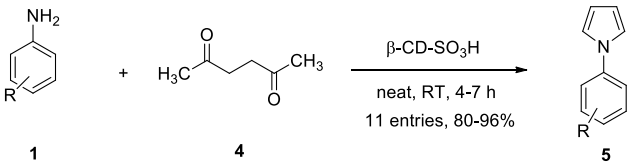


Figure 8.4: β-CD-SO_3H catalyzed pyrrole synthesis *via* Paal–Knorr reaction.

8.3.1.2 Synthesis of imidazo[1,2-*a*]pyridin-3-amine derivatives

Imidazo[1,2-*a*]pyridine -*a*]pyridine skeleton is very common in many commercial drugs such as zolpidem, alpidem, saripidem, zolimidine, olprinone etc. [52, 53]. Various imidazo[1,2-*a*]pyridine derivatives reported to possess a wide range of pharmacological efficacies [54–57]. Because of these huge biological activities, a large number of methods were reported for the synthesis of imidazo[1,2-*a*]pyridin-3-amines involving metal containing catalysts such as $ZnCl_2$ [58], $ZrCl_4$ [59], $SnCl_2$ [60], $LaCl_3{\cdot}7H_2O$ [61], $RuCl_3$ [62], $InCl_3$ [63] etc. under diverse reaction conditions. In 2016, Wu et al. [64] synthesized a series of imidazo[1,2-*a*]pyridin-3-amine derivatives *via* one-pot three-component reactions of aromatic aldehydes (**6**), 2-aminopyridines (**7**), and alkyl

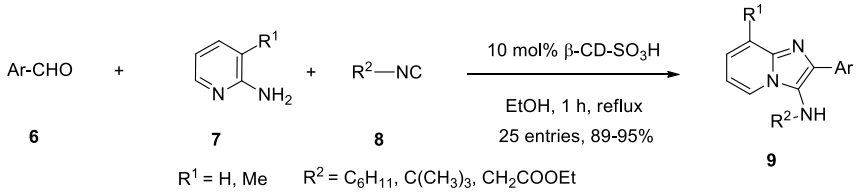


Figure 8.5: β-CD-SO$_3$H catalyzed synthesis of imidazo[1,2-*a*]pyridin-3-amines.

isocyanides (**8**) using a catalytic amount of β-CD-SO$_3$H in ethanol under reflux conditions (Figure 8.5). Under this optimized conditions they obtained comparable yields of the desired products produced by the other metal catalysts. Wide substrate scope, high yields, shorter reaction times, and use of metal-free organocatalyst are some of the salient features of this developed protocol. Plausible mechanism along with the role of the catalyst is demonstrated in Figure 8.6.

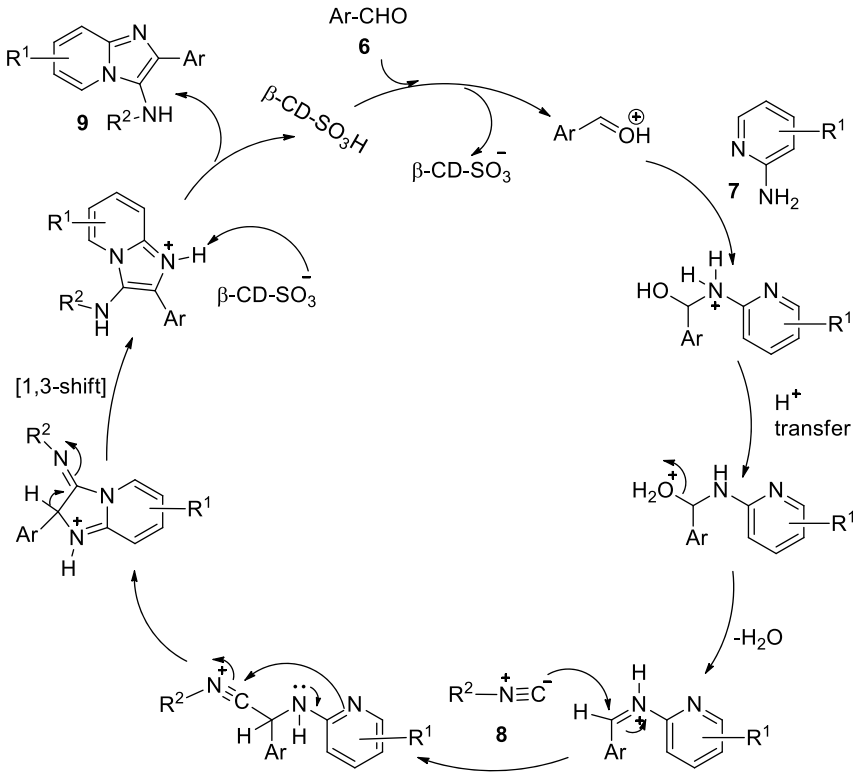


Figure 8.6: Plausible mechanism for the synthesis of imidazo[1,2-*a*]pyridin-3-amines using β-CD-SO$_3$H as catalyst.

8.3.1.3 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one

2,3-Dihydroquinazolin-4(1*H*)-one and its fused analogs have been reported to possess a wide range of biological activities [65–72]. After realizing the importance, a large number of methods were reported for the synthesis of these biologically promising scaffolds involving various homogeneous as well as heterogeneous catalysts such as $Ga(OTf)_3$ [73], silica sulfuric acid [74], montmorillonite K-10 [75], MCM-41-SO_3H [76], $KAl(SO_4)_2{\cdot}12H_2O$ [77], $Al(H_2PO_4)_3$ [78], [bmim]BF_4 [79], etc. Though these reported catalysts produced excellent yields still some of these reported methods suffers from the notable demerits like use of toxic and expensive metal containing catalysts, tedious work up procedure, long reactions, use of organic solvents etc. In 2014, Wu et al. [80] reported a simple, facile metal-free organocatalyzed protocol for the synthesis of a series of 2,3-dihydroquinazolin-4(1*H*)-one derivatives from the reactions of aromatic aldehydes (**6**) and 2-aminobenzamides (**10**) in the presence of a catalytic amount of β-cyclodextrin sulfonic acid in water at ambient temperature (Figure 8.7). Under the same optimized conditions, instead of aldehydes, a number of cyclic as well as acyclic ketones (**12**) were also preceded smoothly and afforded the desired products (**13**) with excellent yields (Figure 8.8). The same series of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**11**/**13**) were also synthesized *via* a one-pot three-component reactions between substituted isatoic anhydride (**14**), amines (**1**) and various aldehydes (**6**) or ketones (**12**) using the same catalysts in aqueous medium at 80 °C (Figure 8.9). It was proposed that the reaction proceeded through the formation of *in situ* generated 2-aminobenzamides (**10**) from the reactions between isatoic anhydride (**14**), amines (**1**). This *in situ* generated 2-aminobenzamides (**10**) on reaction with carbonyl compounds generate the intermediate **15**, which further produces the desired products (**13**) under the catalytic influence of β-CD-SO_3H through cyclization followed by dehydration reaction (Figure 8.10).

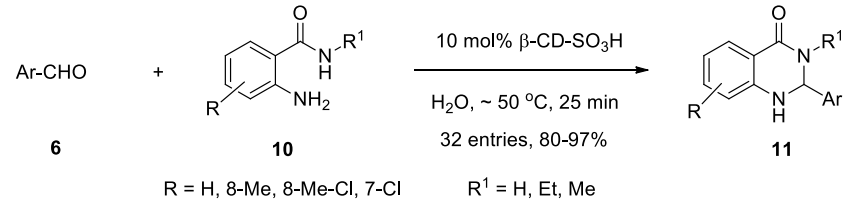


Figure 8.7: β-CD-SO_3H catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones starting from aldehydes and 2-aminobenzamides.

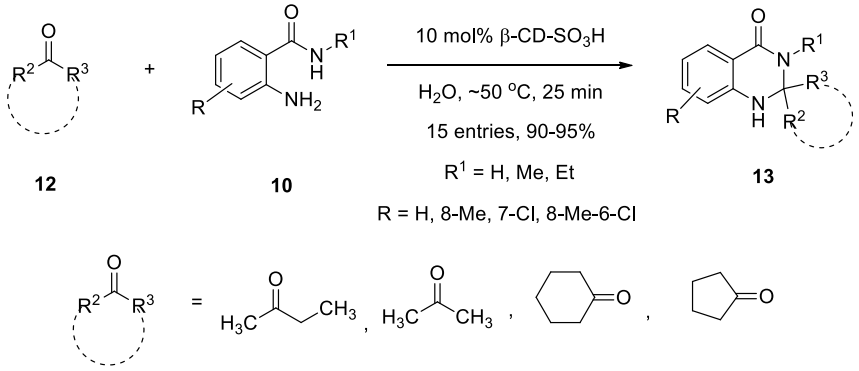


Figure 8.8: β-CD-SO_3H catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones starting from ketones and 2-aminobenzamides.

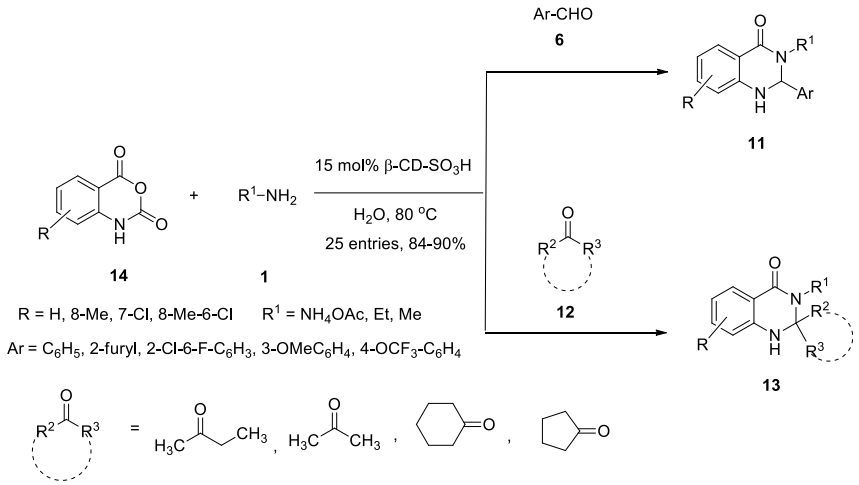


Figure 8.9: β-CD-SO_3H catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones starting from 1*H*-benzo[*d*][1,3]oxazine-2,4-diones.

8.3.1.4 Synthesis of 3,4-dihydro-2*H*-indazolo[2,1-*b*]phthalazinetriones

3,4-Dihydro-1*H*-indazolo[1,2-*b*]phthalazinetriones derivatives are found as a core structural unit in many naturally occurring as well as synthetic bioactive molecules [81]. A number of methods were reported for the synthesis of 3,4-dihydro-1*H*-indazolo [1,2-*b*]phthalazinetrione derivatives employing various homogeneous as well as heterogeneous catalysts such as *p*-TSA [82], dodecylphosphonic acid (DPA) [83], $Ce(SO_4)_2 \cdot 4H_2O$ [84], heteropoly acids [85], solid acids [86], phosphomolybdic acid-silica (PMA-SiO_2) [87] montmorillonite K-10 [88], silicasulfuric acid [89], etc. Though these

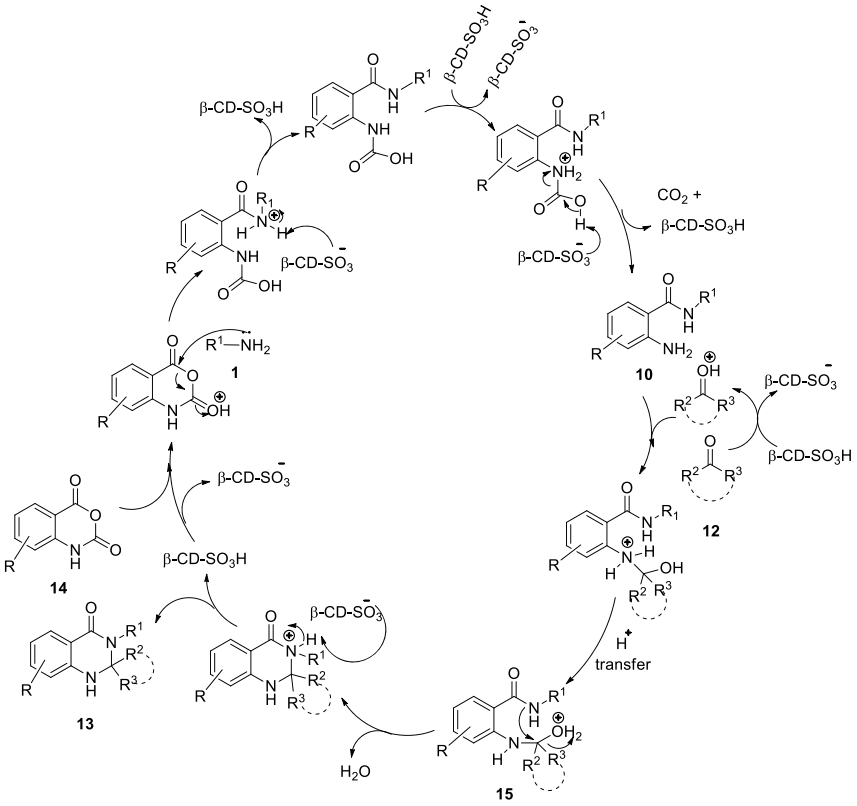


Figure 8.10: Plausible mechanism for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones starting from 1*H*-benzo[*d*][1,3]oxazine-2,4-diones.

catalysts produced the desired products with excellent yields; still some of these methods suffer from notable demerits like expensive and metal containing catalysts, use of organic solvents, harsh reaction conditions, tedious separation procedure, nonreusability of the catalyst etc. In 2015, Atar et al. [90] reported a mild, simple and ecofriendly one-pot three-component protocol for the synthesis of a series of 3,4-dihydro-2*H*-indazolo[2,1-*b*]phthalazinetrione derivatives (**18**) from the reactions of phthalhydrazide (**16**), aromatic aldehydes (**6**), and dimedone (**17**) using a catalytic amount of β-CD-SO_3H as an efficient metal-free organocatalyst under neat conditions at 80 °C (Figure 8.11). When the other conditions remain unchanged, the same path of reactions afforded lesser product by using β-CD as catalyst. Catalytic efficacy of a number of metal catalysts such as $CaCl_2$, SiO_2, $FeCl_3$, $Zn(OTf)_2$, $ZnCl_2$, CuF_2, $CuCl_2$, Li(OTf), $SnCl_2{\cdot}2H_2O$ etc. were also screened but found less effective for this reaction. The catalyst was recovered quantitatively and reused for three successive runs without any notable loss in its catalytic activities. It was proposed that first dimedone (**17**) and aldehydes (**6**) formed the corresponding Knoevenagel condensation products (**19**)

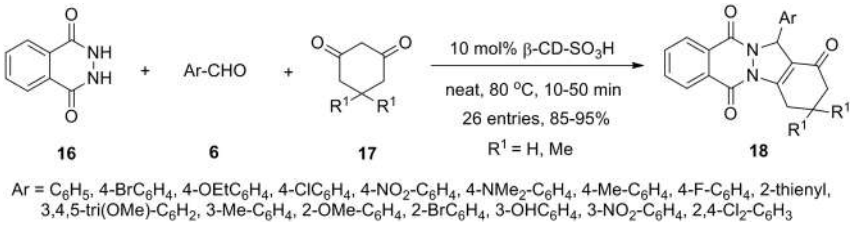


Figure 8.11: β-CD-SO_3H catalyzed synthesis of 3,4-dihydro-2*H*-indazolo[2,1-*b*]phthalazinetriones.

which on reaction with phthalhydrazide (**16**) afforded the desired 3,4-dihydro-2*H*-indazolo[2,1-*b*]phthalazinetrione derivatives (**18**) with excellent yields (Figure 8.12).

8.3.1.5 Synthesis of spiroindolone derivatives by Pictet–Spengler spirocyclisation

In 2017, Urmode et al. [91] developed a simple and aqueous mediated protocol for the synthesis of a series of biologically promising tetrahydrospiro-β-carboline derivatives (**22**) *via* the Pictet–Spengler spirocyclisation reaction between substituted isatins (**20**) and tryptamine (**21**) using a catalytic amount of β-CD-SO_3H as an efficient metal-free organocatalyst at 80 °C (Figure 8.13). The catalyst along with the reaction media was reused for three times without any significant loss in its activity. This was the first report of Pictet–Spengler spirocyclisation reaction in aqueous medium. Before this report the same reaction was carried out by using a number of catalysts in various organic

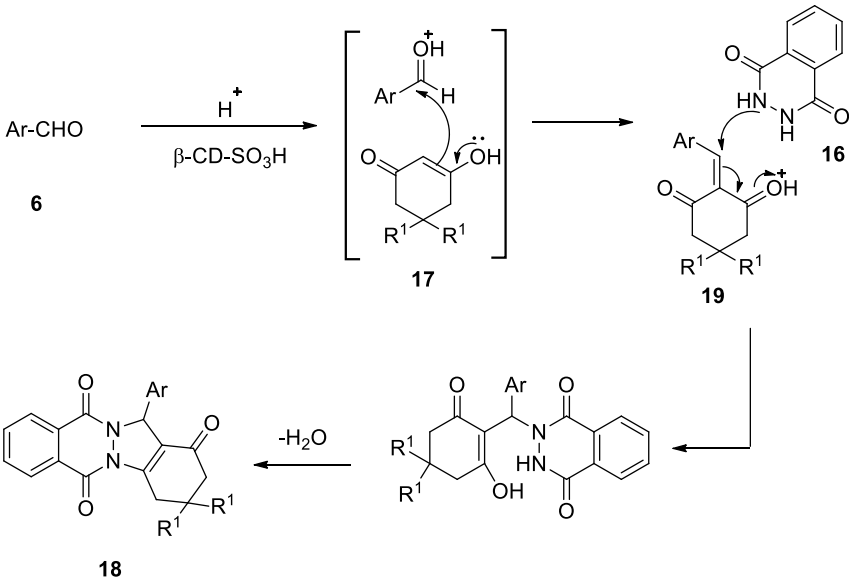


Figure 8.12: Plausible mechanism for the synthesis of 3,4-dihydro-2*H*-indazolo[2,1-*b*] phthalazinetriones using β-CD-SO_3H as catalyst.

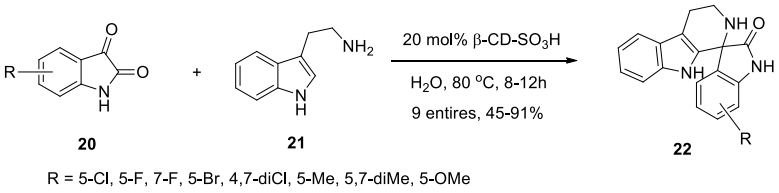


Figure 8.13: β-CD-SO_3H catalyzed synthesis of spiro[indoline-3,1′-pyrido[3,4-*b*]indol]-2-ones.

solvents [92–95]. Under the same optimized conditions, Urmode et al. also synthesized a number of tetrahydrospiro-γ-carboline derivatives (**24**) with moderate to excellent yields by using isotryptamine (**23**) instead of tryptamine (**21**) (Figure 8.14).

8.3.1.6 Synthesis of 1,8-dioxodecahydroacridines

Using a catalytic amount of β-CD-SO_3H as catalyst, a series of 1,8-dioxodecahydroacridines (**26**) was synthesized by Pitchumani and his group [96] *via* one-pot pseudo four-component reactions between one equivalent of aromatic aldehydes (**6**), two equivalents of dimedone (**17**) and one equivalent of ammonium chloride in water at 60 °C (Figure 8.15). Under the same reaction condition, β-CD afforded only 8% of the desired product. By using comparative nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS) studies, they confirmed the involvement of β-CD-SO_3H as catalyst. Catalyst containing the residual reaction medium was recycled for five successive runs. Aldehydes bearing both electrons donating as well as withdrawing substituent proceeded smoothly and afforded the desired products with excellent yields.

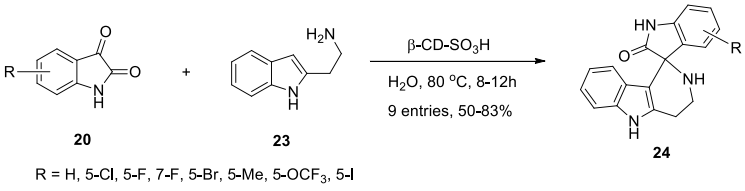


Figure 8.14: β-CD-SO_3H catalyzed synthesis of spiro[indoline-3,1′-pyrido[4,3-*b*]indol]-2-ones.

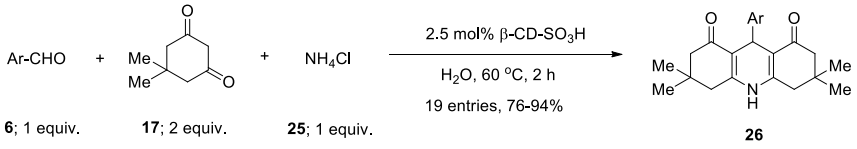
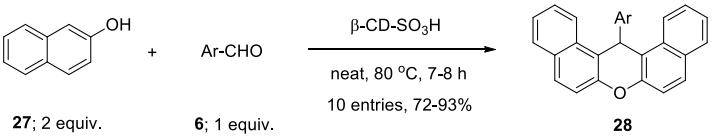


Figure 8.15: β-CD-SO_3H catalyzed synthesis of 1,8-dioxodecahydroacridines in water.

8.3.2 β-CD-SO_3H catalyzed synthesis of *O*-heterocycles

8.3.2.1 Synthesis of 14-aryl-14*H*-benzo[*a*,*j*]xanthenes

Cheraghchi et al. [97] developed a simple and efficient β-CD-SO_3H catalyzed solvent-free protocol for the synthesis of a number of 14-aryl-14*H*-benzo[*a*,*j*]xanthenes *H*-benzo[*a*,*j*]xanthenes (**28**) derivatives *via* one-pot pseudo three-component reactions between two equivalents of β-naphthol (**27**) and one equivalent of aromatic aldehydes (**6**) at 80 °C (Figure 8.16). Aldehydes with both electrons donating as well as withdrawing substituent underwent smoothly and produced the desired products with excellent yields. The plausible mechanism of the reaction is shown in Figure 8.17.



Ar = C_6H_5, 2-ClC_6H_4, 4-BrC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-OMeC_6H_4, 4-MeC_6H_4, 2,4-diMe-C_6H_3, 4-CNC_6H_4, CH=CHC_6H_5

Figure 8.16: β-CD-SO_3H catalyzed synthesis of 14-aryl-14*H*-benzo[*a*,*j*]xanthenes.

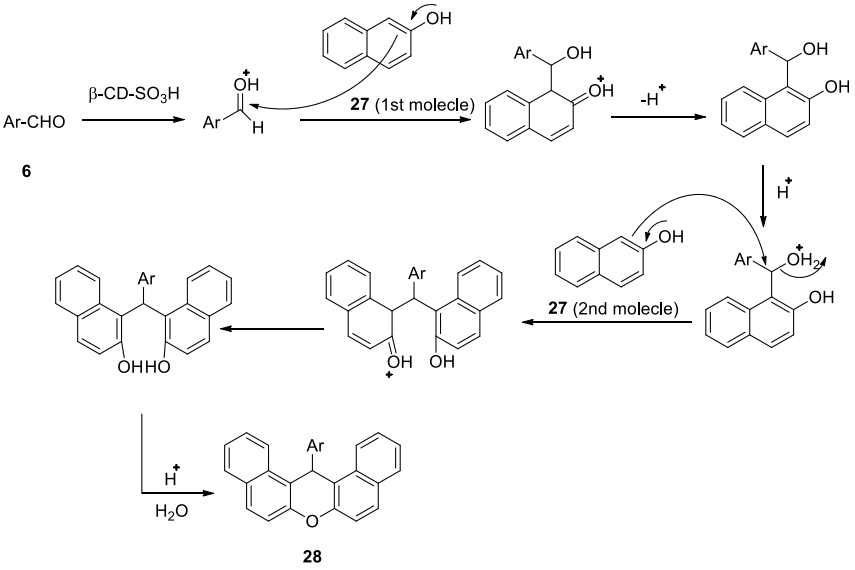
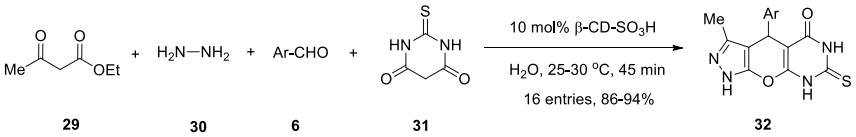


Figure 8.17: Plausible mechanism for the synthesis of 14-aryl-14*H*-benzo[a,j]xanthenes using β-CD-SO_3H acid as catalyst.

8.3.3 β-CD-SO_3H catalyzed synthesis of *N*,*O*-heterocycles

8.3.3.1 Synthesis of pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-ones

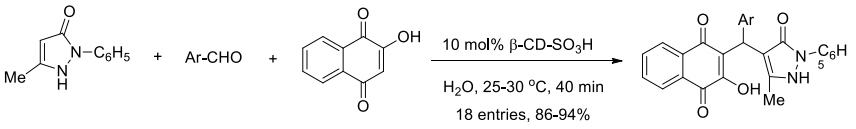
Many pyrazolo fused pyranopyrimidine derivatives showed significant biological activities which include antitubercular, antipyretic, analgesic, antibacterial, anticancer, antiinflammatory, antimicrobial, antifungal etc. activities [98–100]. Patil et al. [101] prepared β-CD-SO_3H by following the reported method and established the inclusion of $-SO_3H$ group in β-CD by ^1H NMR, energy dispersive X-ray analysis (EDAX), Brunauer-Emmett-Teller (BET) surface area analysis, thermogravimetric analysis (TGA) etc. analysis. Using a catalytic amount of the prepared catalyst, they synthesized a series of structurally diverse pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one derivatives (**32**) *via* one-pot four component reactions of ethyl acetoacetate (**29**), hydrazine hydrate (**30**), aromatic aldehydes (**6**), and thiobarbituric acid (**31**) in water at ambient temperature (Figure 8.18). All the reactions were completed just within 45 min. Under the same optimized reaction conditions, along with pyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one derivatives (**32**), a number of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione derivatives (**35**) were also synthesized from the reactions between 5-methyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**33**), aromatic aldehydes (**6**), and 2-hydroxy-1,4-naphthoquinone (**34**) (Figure 8.19). The catalyst along with the residual solvent recycled for four successive runs without any significant loss in its catalytic efficiency. It was proposed that under the influence of β-CD-SO_3H as catalyst, the reaction of aldehydes (**6**) and 2-hydroxy-1,4-naphthoquinone (**34**) produced



29 **30** **6** **31** **32**

Ar = C_6H_5, 4-MeC_6H_4, 3-$OMeC_6H_4$, 4-$OMeC_6H_4$, 2-$OMeC_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-FC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-CNC_6H_4, 4-OHC_6H_4

Figure 8.18: β-CD-SO_3H catalyzed synthesis of pyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidin-5(1*H*)-ones.



33 **6** **34** **35**

Ar = C_6H_5, 4-MeC_6H_4, 3-$OMeC_6H_4$, 3-$OMeC_6H_4$, 2-$OMeC_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-FC_6H_4, 2-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-CNC_6H_4, 4-OHC_6H_4, 3-OMe-4-OHC_6H_3, 3,4-di-$OMeC_6H_3$

Figure 8.19: β-CD-SO_3H catalyzed synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-diones.

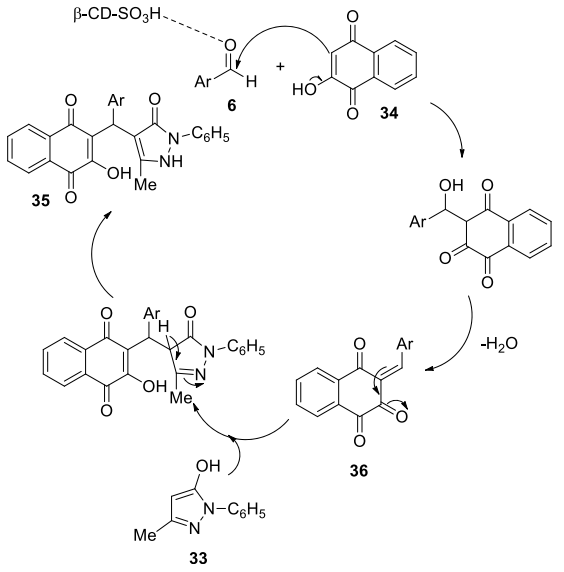


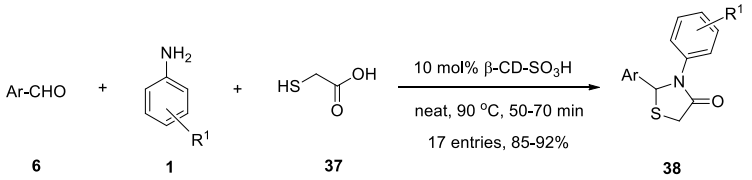
Figure 8.20: Plausible mechanism for the synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-diones.

the intermediate **36** which on reaction with 5-methyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**33**) yielded the desired products (**35**) (Figure 8.20).

8.3.4 β-CD-SO_3H catalyzed synthesis of *N*,*S*-heterocycles

8.3.4.1 Synthesis of 4-thiazolidinones

Many synthetic 4-thiazolidinone derivatives are found to possess a wide range of biological efficacies that include antibacterial [102], anticancer [103], antimalarial [104], antiproliferative [105], antitubercular [106], anticonvulsant [107], anti-inflammatory [108], antidiabetic [109] etc. activities. In 2015, Chaudhari et al. [110] developed a simple and facile protocol for the solvent-free synthesis of a series of 4-thiazolidinones (**38**) *via* one-pot three-component reactions of aromatic aldehydes (**6**), substituted anilines (**1**), and thioglycolic acid (**37**) in the presence of a catalytic amount of β-CD-SO_3H as an efficient metal-free organocatalyst at 90 °C (Figure 8.21). After use, the catalyst was recovered quantitatively and recycled further for five successive runs. During optimization, catalytic activities of a number of other acidic catalysts such as sulfanilic acid, boric acid, citric acid, camphor sulfonic acid, phosphotungstic acid, $HClO_4$–SiO_2, carbon sulfuric acid, xanthan sulfuric acid, silica sulfuric acid etc. were also screened but all of them produced lower yields under solvent-free and heating conditions. Under the same optimized conditions, β-CD as catalyst afforded only 12% yield of the desired product. Probable role of β-CD-SO_3H for this conversation is shown in Figure 8.22.



Ar = 4-ClC$_6$H$_4$, C$_6$H$_5$, 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-OH-C$_6$H$_4$, 2-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 3,4-(OMe)$_2$-C$_6$H$_3$, 3-NO$_2$-C$_6$H$_4$, 2-thienyl
R^1 = H, 4-Cl, 4-Me, 3-Me, 4-F

Figure 8.21: β-CD-SO$_3$H catalyzed synthesis of 4-thiazolidinones under solvent-free conditions.

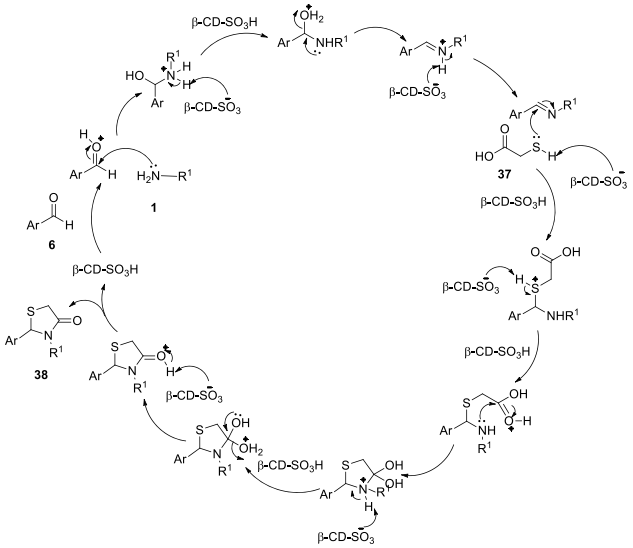


Figure 8.22: Plausible mechanism of the β-CD-SO$_3$H catalyzed synthesis of 4-thiazolidinones.

8.3.5 β-CD-SO$_3$H catalyzed other miscellaneous reactions

8.3.5.1 Esterification of carboxylic acids

Thombal et al. [111] prepared β-CD-SO$_3$H *via* one step hydrothermal carbonization of β-CD with *p*-toluene sulfonic acid under solvent-free conditions at 180 °C. After well characterized the synthesized β-CD derived sulfonic acid functionalized carbonaceous material by using Fourier transform infrared (FTIR), powder X-ray diffraction (PXRD), EDAX, and NH$_3$TPD techniques, they used the same materials as an efficient catalyst for the esterification of various carboxylic acids (**39**) and alcohols (**40**) under solvent-free

conditions which affords the desired products (**41**) with excellent yields at 70 °C (Figure 8.23). The catalysts was recovered successfully and recycled three times without any decrease in product yields. They also successfully employed the same catalyst for the catalytic conversion of carbohydrates to 5-hydroxymethylfurfural [112].

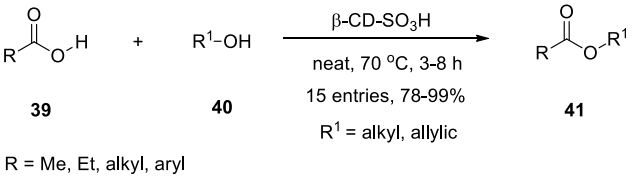


Figure 8.23: β-CD-SO_3H catalyzed esterification of carboxylic acids.

8.3.5.2 Synthesis of 3,3-*bis*(indolyl)indolin-2-ones

Now-a-days, synthesis of 3,3-*bis*(indolyl)indolin-2-one *bis*(indolyl)indolin-2-one derivatives have gained tremendous attention due to its wide range of pharmaceutical activities [113–119]. In 2015, Dalal and his group [120] demonstrated a simple and facile β-CD-SO_3H catalyzed eco-friendly method for the efficient synthesis of 3,3-*bis*(indolyl) indolin-2-ones (**43**) *via* pseudo three-component reactions between one equivalent of substituted isatins (**20**) and two equivalent of substituted indole derivatives (**42**) in water under reflux conditions (Figure 8.24). This developed protocol was so rapid that all the reactions were completed just within 5 min. All the synthesized products were isolated pure just by simple filtration. The catalyst was recovered and recycled for three successive runs without any significant loss in its catalytic activities. Under the same optimized reaction conditions, synthesis of 3-hydroxy-3-(indol-3-yl)indolin-2-ones (**44**) was also accomplished by the equimolecular reactions between substituted isatins (**20**) and indoles (**42**) (Figure 8.25).

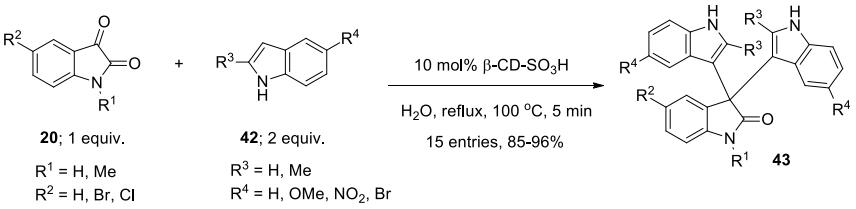


Figure 8.24: β-CD-SO_3H catalyzed synthesis of 3,3-*bis*(indolyl)indolin-2-ones.

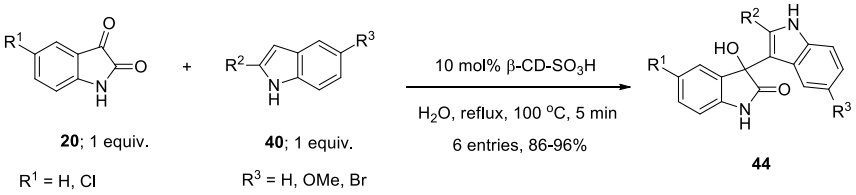
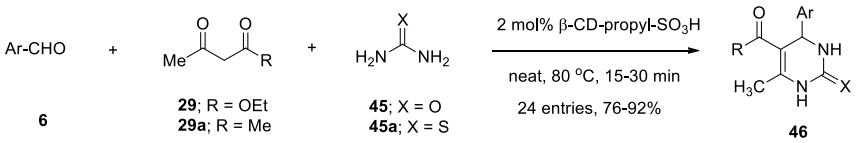


Figure 8.25: β-cyclodextrin sulfonic acid catalyzed synthesis of 3-hydroxy-3-(indol-3-yl)indolin-2-ones in water.

8.4 β-CD-SO_3H catalyzed organic transformations

8.4.1 Synthesis of 3,4-dihydropyrimidones

In 2015, Gong et al. [121] prepared β-CD propyl sulfonic acid β-CD propyl sulfonic acid (β-CD-propyl-SO_3H) from the reaction of β-CD and 1,3-propane sultone in aqueous sodium hydroxide medium. Initially sulfopropyl ether β-CD was formed which on further treatment with acidic resin gave the desired solid β-CD-propyl-SO_3H with excellent yields. After well characterized this by using IR, ^{1}H NMR, ^{13}C NMR and analytical techniques, they employed the same as an efficient catalyst for the synthesis of a series of 3,4-dihydropyrimidones (**46**) *via* one-pot three-component Biginelli reactions between aromatic aldehydes (**6**), ethyl acetoacetate (**29**)/acetyl acetone (**29a**), and urea (**45**)/thiourea (**45a**) under solvent-free conditions at 80 °C (Figure 8.26). They synthesized 24 different derivatives of 3,4-dihydropyrimidones (**46**) with excellent yields within just 30 min. Solid catalyst was recovered quantitatively and recycled for six successive runs without any notable loss in the product yields. It is noteworthy to mention that, previously. in 2011, the same batch of Biginelli reactions were also carried out by Asghari et al. [34] employing β-CD-SO_3H as catalyst which reported to take longer time (2 h) under solvent-free conditions even at 100 °C (Figure 8.27).



Ar = C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-OHC_6H_4, 4-$OMeC_6H_4$, 4-$N(Me)_2C_6H_4$,

Figure 8.26: β-CD-propyl-SO_3H catalyzed synthesis of 3,4-dihydropyrimidones under solvent-free conditions at 80 °C.

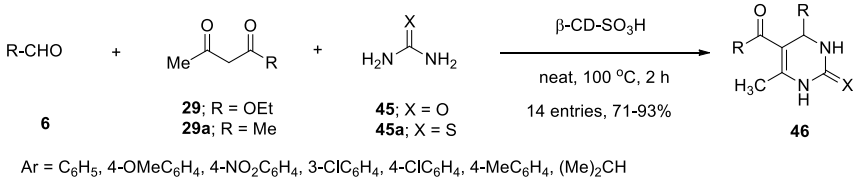


Figure 8.27: β-CD-SO_3H catalyzed synthesis of 3,4-dihydropyrimidones under solvent-free conditions at 100 °C.

8.4.2 Synthesis of 1,2,4,5-tetrasubstituted imidazoles

On the same year, following the same procedure Ran et al. [122] also prepared and well characterized β-CD-SO_3H. Using just 2 mol% of the same metal-free solid catalyst, they synthesized a number of 1,2,4,5-tetrasubstituted imidazoles (**49**) *via* one-pot four-component reactions of benzil (**47**), aromatic aldehydes (**6**), ammonium acetate (**48**), and amines (**1**) under solvent-free conditions at 80 °C (Figure 8.28). After use, the same catalyst was recovered and recycled for successive runs without any decrease in product yields.

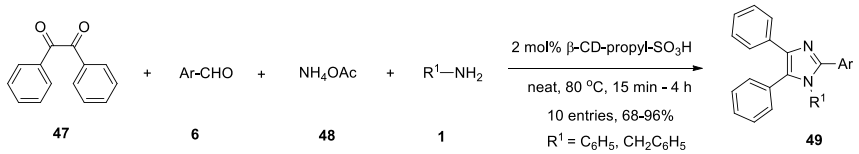
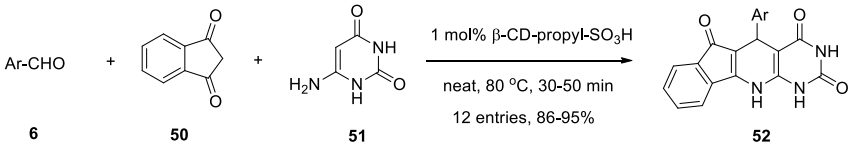


Figure 8.28: β-CD-propyl-SO_3H catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles.

8.4.3 Synthesis of indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-triones

In 2016, Sudhan et al. [123] employed just 1 mol% β-CD-propyl-SO_3H as an efficient catalyst for the one-pot three-component synthesis of a series of indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine-trione derivatives (**52**) from the reactions of aromatic aldehydes (**6**), 1,3-indandione (**50**), and 6-aminouracil (**51**) under solvent-free conditions at 80 °C (Figure 8.29). All the reactions were completed just within 50 min. Aldehydes with both electrons donating as well as electron withdrawing substituent afforded the desired products with excellent yields. During optimization it was found that β-CD afforded 32% of the desired product after 1 h. Other SO_3H catalyst such as methanesulfonic acid and *para*-toluenesulfonic acid produced 5-(4-fluorophenyl)-5,11-dihydro-1*H*-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6-trione with only 35 and 38% yield respectively. Figure 8.30 depicted the plausible mechanism of the conversation. It was proposed that

under the catalytic influence of β-CD-propyl-SO_3H, aromatic aldehydes (**6**) reacts with 1,3-indandione (**50**) to generate the corresponding Knoevenagel adduct (**53**). Then 6-aminouracil (**51**) undergoes Michael type addition reaction with this intermediate (**53**) and produced another intermediate (**54**) which on intramolecular condensation followed by dehydration afforded the desired product **52**.



Ar = C_6H_5, 2-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 3-BrC_6H_4, 2-FC_6H_4, 3-$NO_2C_6H_4$

Figure 8.29: β-CD-propyl-SO_3H catalyzed synthesis of indeno[2′,1′:5,6]pyrido [2,3-*d*]pyrimidine-triones.

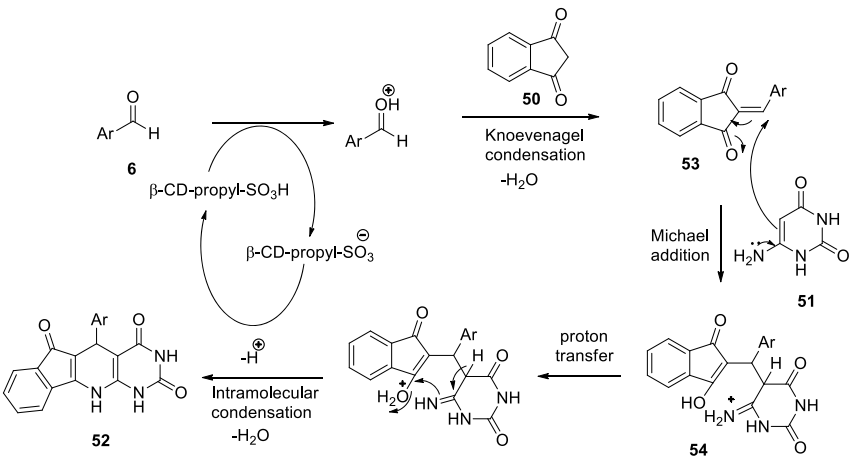


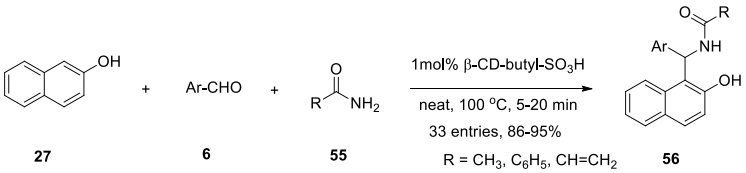
Figure 8.30: Plausible mechanism of the β-CD-propyl-SO_3H catalyzed synthesis of indeno[2′,1′:5,6] pyrido[2,3-*d*]pyrimidine-triones.

8.5 β-CD-butyl-SO_3H catalyzed organic transformations

8.5.1 Synthesis of 1-amidoalkyl-2-naphthols

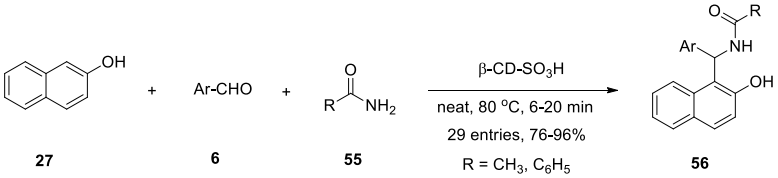
A huge number of catalysts were employed for the synthesis of 1-amidoalkyl-2-naphthols (**56**) under various reactions conditions. Among these reported methods,

majority of these protocols involve the use of metal containing catalyst such as $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [124], $Fe(HSO_4)_3$ [125], MoO_3-ZrO_2 [126], Fe_3O_4-CNTs [127], $H_4SiW_{12}O_{40}$/TPI-MCM-41 [128], $H_3PW_{12}O_{40}$ [129], AgNPs [130], Co(II) Schiff base complex [131], zinconocene dichloride [132], and SO_3H-MCM-41@$NiFe_2O_4$ [133] etc. In 2015, by using 1,4-propane sultone instead of 1,3-propane sultone, Gong, et al. [134] also prepared β-CD-butyl-SO_3H by following the same procedure as reported earlier [34]. Using just 1 mol% of this newly synthesized catalyst they were able to synthesize a series of 1-amidoalkyl-2-naphthols (**56**) *via* one-pot three-component reactions of β-naphthol (**27**), aromatic aldehydes (**6**), and amides (**55**) under solvent-free conditions at 100 °C (Figure 8.31). After first run, the catalyst was recovered and recycled for five successive runs with almost same catalytic efficiency. Later on, in 2017, Pitchumani and his group [135] prepared β-CD-SO_3H and using this as an efficient catalyst they carried out the same batch of reactions which afforded 1-amidoalkyl-2-naphthols (**56**) with excellent yields under solvent-free conditions at 80 °C (Figure 8.32). Both acetamide as well as benzamide reacted smoothly with various substituted aldehydes and β-naphthol to yield the desired products within just 20 min. They were also able to recover the catalyst quantitatively and reused for five successive runs without any notable loss in its catalytic efficiency.



Ar = C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 2,4-Cl_2-C_6H_4, 4-Br-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4

Figure 8.31: β-CD-butyl-SO_3H catalyzed synthesis of 1-amidoalkyl-2-naphthols under solvent free conditions at 100 °C.



Ar = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-FC_6H_4, 3-OH-C_6H_4, 3,5-$(OMe)_2$-C_6H_3, 2-Me-C_6H_4, 2-OH-C_6H_4, 3,4-$(OMe)_2$-C_6H_3, 3-OMe-4-OH-C_6H_3, 3,4-methylenedioxy-6-NO_2-C_6H_2, 2-$NO_2C_6H_4$, 3-MeC_3H_6, 3,5-$(OMe)_2$-4-OH-C_6H_3, CH_3, 3-$OMeC_6H_4$, C_5H_4N

Figure 8.32: β-CD-SO_3H catalyzed synthesis of 1-amidoalkyl-2-naphthols under solvent free conditions at 80 °C.

8.6 Conclusions

Development of new synthetic protocol for various organic transformations using metal-free organocatalysts is one of the thrusting areas in the 21st Century. Among many others, during last one decade, sulfonated β-CD have gained considerable attention as efficient, metal-free, reusable organocatalysts. In the laboratory, β-CD-SO_3H can be synthesized easily by the sulfonation of β-CD using chlorosulfonic acid. Various biologically promising heterocyclic scaffolds were synthesized by using a catalytic amount of sulfonated β-CD under mild and ecofriendly conditions. This fascinating organocatalyst was found efficient to carry out a number of name reactions *viz*. Clauson–Kaas reaction, Pictet–Spengler spirocyclisation reaction, Biginelli reaction, Paal–Knorr reaction etc. In many occasions, after completion of the reaction, this supramolecular organocatalyst was recovered and reused for further runs without any loss in its catalytic activities. Therefore, we strongly believe that this review will surely attract the organic methodologists searching for an efficient, supramolecular, less toxic, metal-free, and reusable organocatalyst.

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Research funding: None declared.
Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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9 Baker's yeast (*Saccharomyces cerevisiae*) catalyzed synthesis of bioactive heterocycles and some stereoselective reactions

Abstract: *Saccharomyces cerevisiae*, commonly known as baker's yeast, has gained significant importance as a mild, low-cost, environmentally benign biocatalyst. Initially it was mostly employed as an efficient catalyst for the enantioselective reduction of carbonyl compounds. Over the last decade, baker's yeast has found versatile catalytic applications in various organic transformations. Many multicomponent reactions were also catalyzed by baker's yeast. Various heterocyclic scaffolds with immense biological activities were synthesized by employing baker's yeast as catalyst at room temperature. In this communication, we have summarized baker's yeast catalyzed various organic transformations focusing primarily on heterocyclic synthesis.

Keywords: baker's yeast; biocatalyst; heterocycles; room temperature reaction; *Saccharomyces cerevisiae*; sustainable developments.

9.1 Introduction

Metal-free organocatalysts are regarded as an important tool to develop sustainable reaction protocols [1–6]. Along with various organocatalysts, during last two decades, enzymes and microorganisms have gained huge attention as a mild, environmentally benign and stereoselective biocatalyst in organic synthesis [7]. Now-a-days, whole-cell biocatalysis finds many applications in organic transformations [8, 9]. Among the biocatalysts used, baker's yeast (*Saccharomyces cerevisiae*), a single-cell microorganism, showed high catalytic activity against diverse organic transformation. The strains of yeast commonly used in baking bread are generally known as baker's yeast. In ancient Egypt, baker's yeast was first employed to ferment sugar in bread dough and now it has become an important, cheap, commercially available substance for food processing [10]. In some occasions baker's yeast was used immobilizing with other supports such as gelatin gel, calcium alginate, montmorillonite K10, chrysotile, *etc*.

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Sahoo and Banik [11] in their review highlighted the production of baker's yeast by aerobic fermentation of selected strains of *S. cerevisiae*. Servi [12] reported a review related to the applications of baker's yeast as reagent in organic synthesis. Csuk and Glaenzer [13] summarized the literature related to the applications of baker's yeast as catalyst till 1991. In 2019, Santra [14] compiled the literature of multicomponent reactions catalyzed by baker's yeast. Due to the wide availability, easy to handle, low cost, ecofriendly nature, nonpathogenic, and wide substrate acceptability made this biocatalyst a useful substrate for various biotransformations. Initially bakers' yeast was employed for the asymmetric reduction of β-keto esters [15, 16], reduction of ketones [17], α-keto esters [18], β-keto phenyl sulphides [19] or α,β-unsaturated carbonyl compounds [20], reduction of nitro compounds to the corresponding amines [21, 22] asymmetric reduction of nitro olefins [23], reduction of the C=C bond [24], acyloin condensation reaction [25], oxidation of sulfide to sulfoxide [26] and many more [27–30] purposes. These reported conversations are comparatively simple and straightforward in nature. Many of them were carried out in aqueous medium. Recently, from various studies, it has been well established that bakers' yeast can also be used to carry out various multicomponent organic transformations even for the synthesis of structurally diverse heterocyclic scaffolds.

In this communication we have summarized the recent developments of baker's yeast catalyzed various organic transformations.

9.2 Baker's yeast catalyzed synthesis of heterocyclic scaffolds

9.2.1 Baker's yeast catalyzed synthesis of *N*-heterocycles

9.2.1.1 Synthesis of fully substituted pyridine derivatives

Naturally occurring as well as various synthetic fully substituted pyridine derivatives are found to possess a wide range of therapeutic efficacies which include antibacterial [31], anticancer [32], antiviral [33], antifungal [34], antihepatitis [35] *etc.* activities. Moreover some of the pyridine derivatives showed prominent activity against Parkinson disease [36]. Few of them can be used as efficient potassium channel openers [37]. Realizing the importance of these scaffolds a number of methods were reported employing various homogeneous as well as heterogeneous catalysts [38–47]. These reported methods definitely have certain merits still many of them suffer from some common disadvantages like use of metal containing catalysts, long reaction times, low yields, harsh reaction conditions *etc.* In 2017, Chavan *et al.* [48] synthesized a series of 2-amino 4-aryl-3,5-dicyano-6-phenyl thiopyridine derivatives (**4**) from one-pot pseudo four-component reactions of one equivalent aromatic aldehydes (**1**),

two equivalent malononitrile (**2**) and one equivalent thiophenol (**3**) using Baker's yeast as an efficient metal-free enzymatic catalyst in ethanol at room temperature (Figure 9.1). All the reactions were completed within 40 min and produced the desired products with excellent yields (82–93%). Aldehydes with both electron donating as well as withdrawing substituent underwent smoothly and afforded the targeted products. It was proposed that the strong nucleophilic as well as electrophilic active sites of the enzyme residues such as histidine, serine, aspartate anion *etc.* may take part in the catalytic process. Plausible mechanism of this conversation is depicted in Figure 9.2.

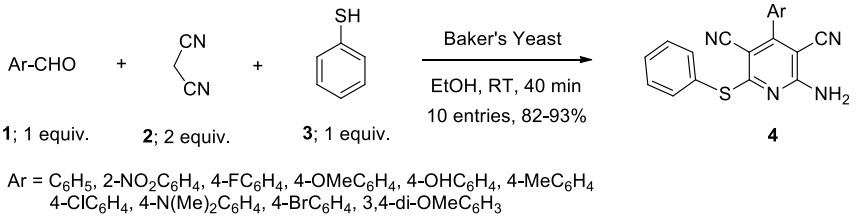


Figure 9.1: Baker's yeast catalyzed synthesis of 2-amino 4-aryl-3,5-dicyano-6-phenyl thiopyridines at room temperature.

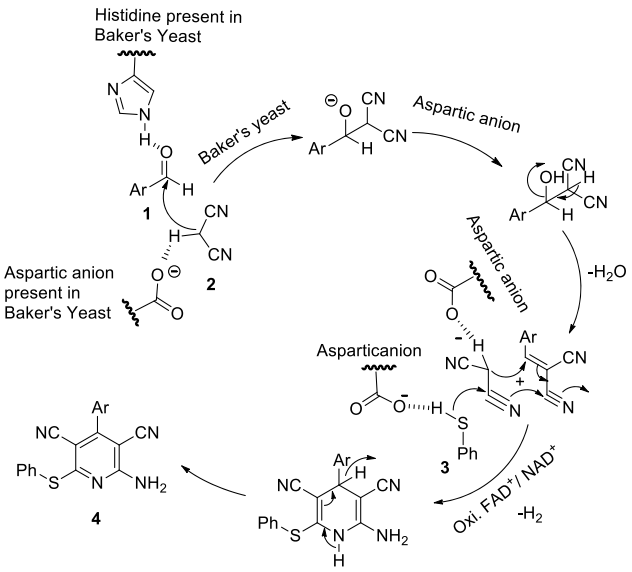


Figure 9.2: Plausible mechanism for the synthesis of 2-amino 4-aryl-3,5-dicyano-6-phenyl thiopyridines using baker's yeast as catalyst.

9.2.1.2 Synthesis of highly substituted dihydropyridyl derivatives

The metal-free catalytic synthesis of dihydropyridines *via* Hantzsch reaction constitutes an important aspect [49]. In 2005, Lee [50] demonstrated baker's yeast catalyzed a mild and simple Hantzsch reaction protocol for the efficient synthesis of highly substituted dihydropyridyl derivatives (**7a,7b**) from one-pot pseudo three-component reactions of two equivalents of β-ketoesters (**5**), one equivalent of *in situ* generated acetaldehyde (**1**a) and one equivalent of ammonium acetate (**6**) in phosphate buffer solution (pH 7.0) at room temperature (Figure 9.3). It was proposed that under the influence of baker's yeast, acetaldehyde generated *in situ* by the glycolysis of D-glucose (**8**) through the formation of pyruvate (**9**) at room temperature. Under the same baker's yeast catalyzed reaction conditions 3-cyano-1,4-dihydropyridines (**11a**,**11b**) were also synthesized with moderate yields from the unimolecular reactions of β-ketoesters (**5**), *in situ* generated acetaldehyde (**1**a) and 3-amino crotonitrile (**10**) at room temperature (Figure 9.3).

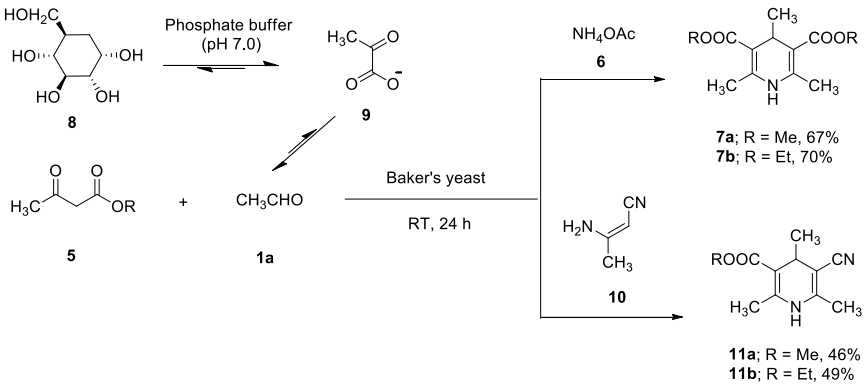


Figure 9.3: Baker's yeast catalyzed synthesis of highly substituted dihydropyridyl derivatives.

9.2.1.3 Synthesis of 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates

In 2007, Kumar and Maurya [51] developed a new catalytic strategy involving fermentation of baker's yeast with D-glucose in the presence of phosphate buffer (pH 7.0). Using this strategy they synthesized a series of 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate derivatives (**13**) from one-pot four-component reactions of β-ketoesters (**5**), ammonium acetate (**6**), aromatic aldehydes (**1**), and dimedone (**12**) under the catalytic influence of prefermented baker's yeast (Figure 9.4). Reaction mixtures were stirred at room temperature for 24 h and afforded the desired products with moderate to good yields. Interestingly, like previous reported method (Figure 9.3), *in situ* generated acetaldehyde didn't take part in the reaction. This may be

due to the higher reactivity of aromatic aldehydes. In absence of the catalyst 2,2′-(arylmethylene)*bis*(3-hydroxy-5,5-dimethylcyclohex-2-enones) were formed as major products. This indicates baker's yeast has a definite role for the formation of the desired products.

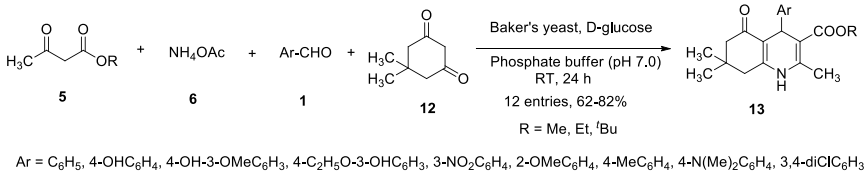


Figure 9.4: Baker's yeast catalyzed synthesis of 5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylates at room temperature.

9.2.1.4 Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones

In the same year, Kumar and Maurya [52] employed the same strategy, i.e. pre-fermented baker's yeast as catalyst, for the synthesis of a number of biologically promising 3,4-dihydropyrimidin-2-(1*H*)-one derivatives *via* the Biginelli reactions between aromatic aldehydes (**1**), β-ketoesters (**5**) and urea (**14**) or thiourea (**14a**) at room temperature (Figure 9.5). During optimization it was observed that prefermented baker's yeast is essential for the efficient synthesis of the desired products. Moreover, the same batch of the reactions produced very trace amount of the desired products in absence of baker's yeast.

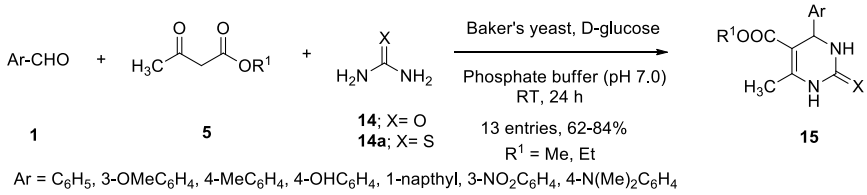


Figure 9.5: Baker's yeast catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones at room temperature.

9.2.1.5 Synthesis of N-substituted 1,8-dioxodecahydroacridines

In 2016, Chate *et al.* [53] developed a facile and ultrasound-assisted protocol for the efficient synthesis of *N*-substituted decahydroacridine-1,8-diones (**18**,**19**) *via* one-pot three-component reactions between two equivalents of dimedone (**12**), one equivalent of aromatic or aliphatic aldehyde (**1**) and one equivalent of substituted anilines (**16**) or

isonicotinohydrazide (**17**) using baker's yeast as catalyst in acetonitrile at room temperature (Figure 9.6). After completion of the reaction the catalyst was recovered and recycled for three further runs without any significant loss in its catalytic activities. In absence of ultrasound the same batch of reactions took longer times and generated very poor yields. Aldehydes with both electron donating as well as withdrawing substituent underwent smoothly and afforded the desired products in excellent yields.

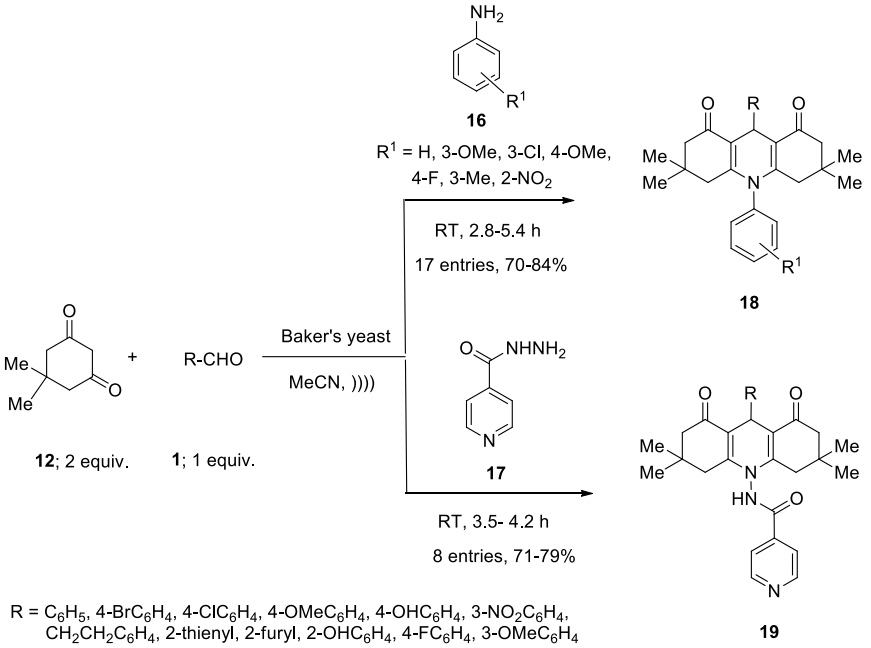


Figure 9.6: Baker's yeast catalyzed synthesis of *N*-substituted 1,8-dioxodecahydroacridines.

9.2.1.6 Synthesis of benzimidazoles quinoxaline derivatives

Beheshtiha *et al.* [54] synthesized a series of benzimidazole derivatives (**23**) in excellent yields starting from *o*-phenylenediamine (**20**) and aldehydes (**1**) using a catalytic amount of baker's yeast in aqueous medium at room temperature (Figure 9.7). Aldehydes with both electron donating as well as withdrawing substituent underwent smoothly and afforded the desired products in excellent yields. Under the same optimized reaction conditions they were also able to synthesize 2,3-diarylquinoxalines (**24**) and acenaphtho[1,2-*b*]quinoxalines (**25**) from the reactions of *o*-phenylenediamines (**20**) and benzils (**21**,**21a**) or acenaphthylene-1,2-dione (**22**), respectively. Under these conditions, formation of quinoxalines was accomplished within just 15 min. Navarro-Ocaña *et al.* [55] synthesized 2-methyl-6-substituedbenzimidazoles (**23a**) with

moderate yields starting from 2′-nitroacetanilides (**26**) in the presence of a catalytic amount of baker's yeast at 30 °C (Figure 9.8). Under slightly acidic conditions (pH 4) baker's yeast reduced 2′-nitroacetanilides (**26**) to the corresponding hydroxylamines (**27**) which produced the desired products *via* the intramolecular cyclization reaction. Along with **23a**, 2-methyl-1*H*-benzo[*d*]imidazol-1-ols (**23b**) were also formed as minor products. In 2017, using baker's yeast as catalyst, Lalit *et al.* [56] synthesized 2-arylquinoxalines (**29**) from the reactions of 2-chloroacetophenones (**28**) and *o*-phenylenediamine (**20**) in acetonitrile at room temperature (Figure 9.9).

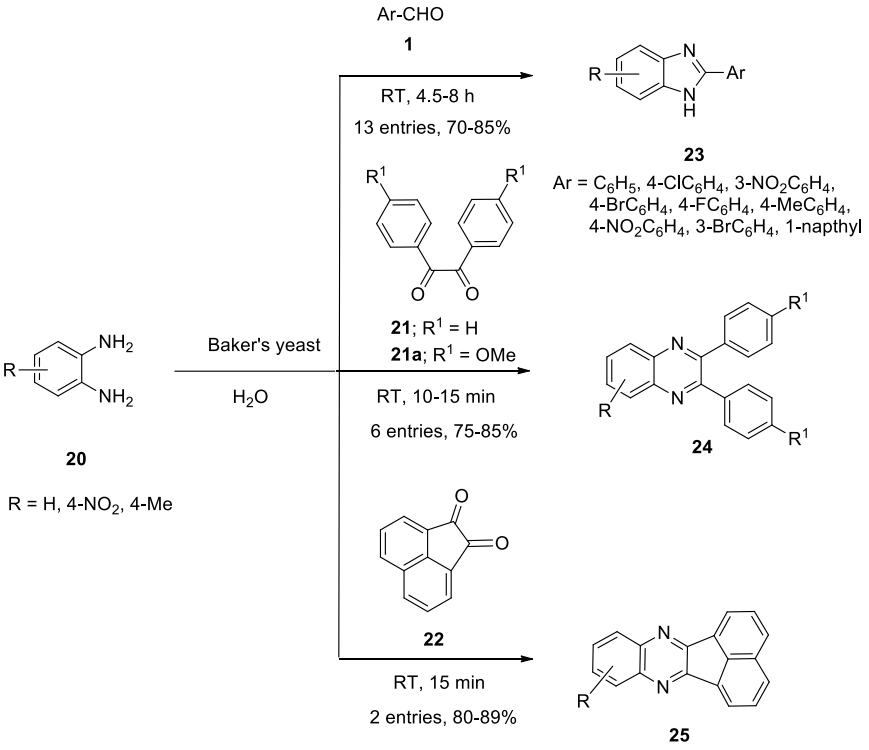


Figure 9.7: Baker's yeast catalyzed synthesis of benzimidazoles and quinoxaline derivatives.

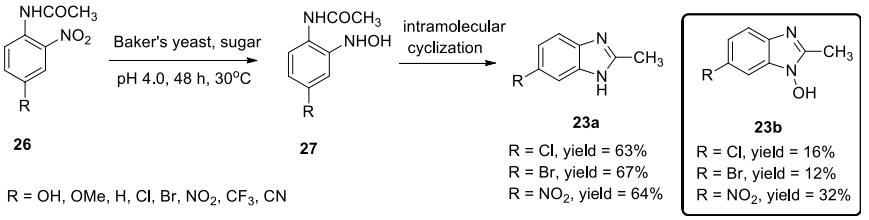


Figure 9.8: Proposed mechanism for the formation of compounds 2-methyl-6-substituedbenzimidazoles.

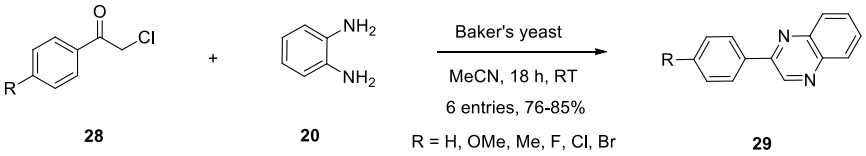


Figure 9.9: Baker's yeast catalyzed synthesis of 2-arylquinoxalines at room temperature.

9.2.1.7 Synthesis of isoindolo[2,1-a]quinazoline derivatives

Avalani *et al.* [57] reported a simple, facile and ultrasound-assisted protocol for the efficient synthesis of a series of isoindolo[2,1-*a*]quinazoline derivatives (**32**) *via* one-pot three-component reactions of isatoic anhydride (**30**), salicylic acid (**31**), and various aromatic or aliphatic amines (**16**) in the presence of a catalytic amount of baker's yeast in tetrahydrofuran (THF) at 30 °C (Figure 9.10). In absence of ultrasound the same batch of reactions took longer times and yielded lesser products.

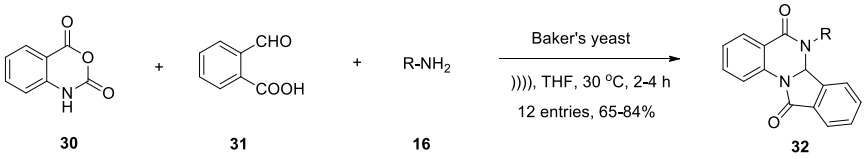


Figure 9.10: Baker's yeast catalyzed synthesis of isoindolo[2,1-*a*]quinazoline derivatives.

9.2.1.8 Synthesis of 2-aryl-2H-benzotriazoles

Baik *et al.* [58] demonstrated baker's yeast promoted intramolecular cyclization reaction of 2-((2-nitrophenyl)diazenyl)phenols (**33**) which afforded the intermediate *N*-oxides (**32**) within 4 h under basic medium at 89-85 °C. When the reactions were further carried out for 40 h the intermediate *N*-oxides (**34**) reduced and afforded the corresponding 2-aryl-2*H*-benzotriazoles (**35**) in excellent yields (Figure 9.11).

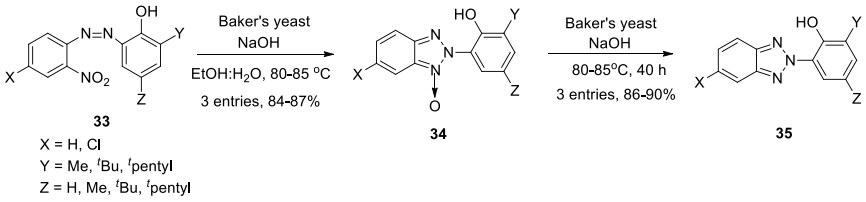


Figure 9.11: Baker's yeast catalyzed synthesis of synthesis of 2-aryl-2*H*-benzotriazoles.

9.2.1.9 Synthesis of 2-arylimidazo[1,2-a]pyridines

Baker's yeast catalyzed synthesis of 2-arylimidazo[1,2-*a*]pyridines (**37**) was achieved by the reactions of 2-chloroacetophenones (**28**) and 2-aminopyridine (**36**) in acetonitrile at room temperature (Figure 9.12) [56]. All the products were isolated pure in excellent yields.

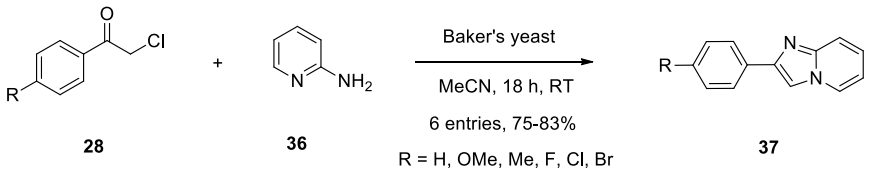


Figure 9.12: Baker's yeast catalyzed synthesis of 2-arylimidazo[1,2-*a*]pyridines at room temperature.

9.2.2 Baker's yeast catalyzed synthesis of *O*-heterocycles

9.2.2.1 Synthesis of indolyl or pyrrolyl chromenes

Singh *et al.* [59] prepared a series of indolyl chromene derivatives *viz.* 2-amino-4-(indol-3-yl)-4*H*-chromene-3-carbonitrile (**41**) and 3-amino-1-(indol-3-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile (**42**) from one-pot three-component reactions of indoles (**38**), malononitrile (**2**), and salicylaldehyde (**39**) or 2-hydroxynaphthaldehyde (**40**), respectively, in the presence of a catalytic amount of baker's yeast in water at room temperature (Figure 9.13). All the reactions were underwent smoothly and afforded the desired products in excellent yields. Under the same optimized reaction conditions they were also able to synthesize 2-amino-4-(1*H*-pyrrol-2-yl)-4*H*-chromene-3-carbonitrile (**44**) and 3-amino-1-(1*H*-pyrrol-2-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile (**45**) from the reactions of pyrrole (**43**), malononitrile (**2**), and salicylaldehyde (**39**) or 2-hydroxynaphthaldehyde (**40**), respectively, (Figure 9.14). Mild reaction conditions, good yields, environmental friendliness, use of water as solvent are some of the major advantages of this developed protocol.

9.2.2.2 Synthesis of 2-amino-3-cyano-pyrans and pyran annulated scaffolds

2-Amino-3-cyano-pyrans and pyran annulated heterocycles possess significant biological efficacies including antibacterial, antiviral, antitumor, spasmolytic, and antianaphylactic activities [60–66]. In 2011, Pratap *et al.* [67] synthesized fully functionalized 2-amino-3-cyano-pyran derivatives (**46**) from the reactions of aromatic aldehydes (**1**), malononitrile (**2**), and β-ketoesters (**5**) using a catalytic amount of baker's yeast in dimethylacetamide at room temperature (Figure 9.15). All the products

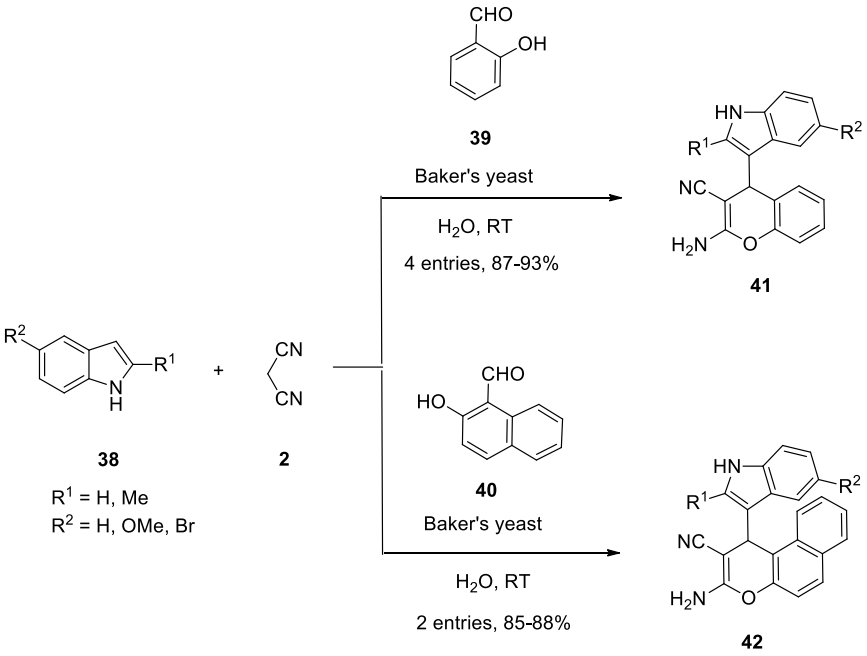


Figure 9.13: Baker's yeast catalyzed synthesis of indolyl chromenes in water.

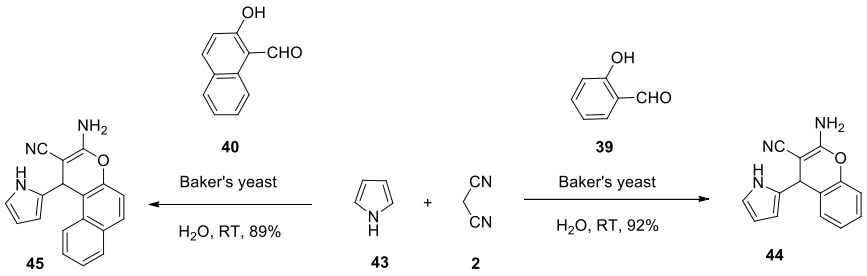
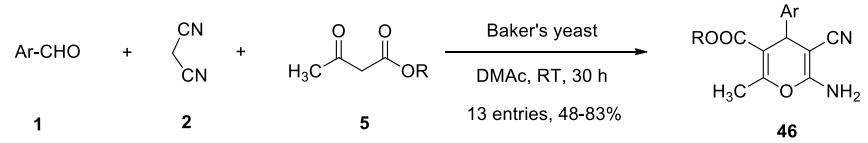


Figure 9.14: Baker's yeast catalyzed synthesis of pyrrolyl chromenes in water.

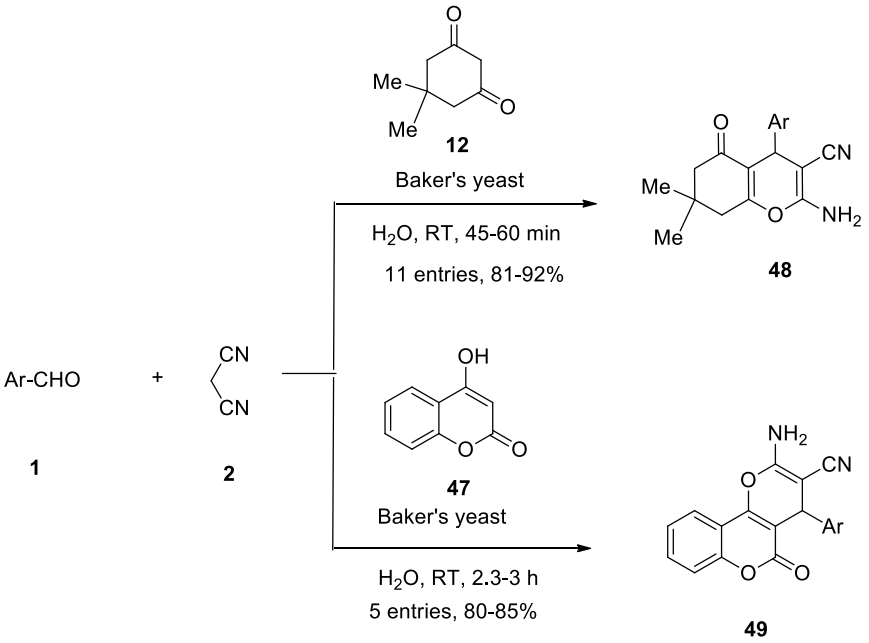
were isolated just by simple filtration. Later on, in 2013, Saha and Pal [68] developed an efficient baker's yeast catalyzed facile protocol for the synthesis of a series of structurally diverse pyran annulated scaffolds *viz.* 2-amino-7,7-dimethyl-5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles (**48**) and 2-amino-5-oxo-4-aryl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitriles (**49**) *via* one-pot three-component reactions of various aromatic aldehydes (**1**), malononitrile (**2**), and dimedone (**12**) or 4-hydroxycoumarin (**47**) in aqueous medium at room temperature (Figure 9.16). Aldehydes with both electron donating as well as withdrawing substituent underwent smoothly and afforded the desired products in excellent yields. All the products were

isolated just by simple filtration; no tedious chromatographic separation was required. Synthesis of compounds **48** was accomplished within just 1 h.



Ar = C_6H_5, 4-$OMeC_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-OHC_6H_4, 4-FC_6H_4, 3-pyridyl
R = Me, Et

Figure 9.15: Baker's yeast catalyzed synthesis of 2-amino-3-cyano-pyrans at room temperature.



Ar = C_6H_5, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-$N(Me)_2C_6H_4$, 4-ClC_6H_4, 4-CNC_6H_4, 2-ClC_6H_4

Figure 9.16: Baker's yeast catalyzed synthesis of pyran annulated heterocycles in water.

9.2.3 Baker's yeast catalyzed synthesis of *N,O*-heterocycles

9.2.3.1 Asymmetric cycloaddition of nitrileoxides

Rao *et al.* [69] demonstrated baker's yeast catalyzed asymmetric cycloaddition of aryl substituted nitrileoxides (**50**) to vinyl pyridines (**51**) which afforded the corresponding

optically active 2-isoxazolines (**52**) in good to excellent yields. The stereoselective was enhanced by adding β-cyclodextrin as an additional binding cavity along with baker's yeast as catalyst (Figure 9.17).

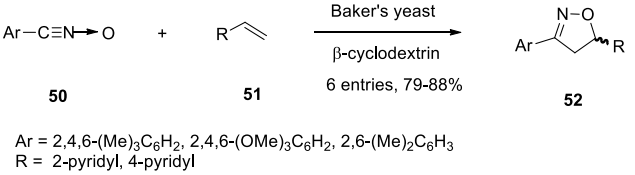


Figure 9.17: Baker's yeast catalyzed asymmetric cycloaddition of nitrileoxides to vinylpyridine.

9.2.4 Baker's yeast catalyzed synthesis of *N,S*-heterocycles

9.2.4.1 Synthesis of 1,3-thiazolidin-4-one-5-acetic acid derivatives

Chavan *et al.* [70] developed a simple, rapid, and ultrasound-assisted protocol for the synthesis of biologically promising 2-[benzylidenehydrazono]-1,3-thiazolidin-4-one-5-yl-acetic acid derivatives (**56**) *via* one-pot three-component reactions of maleic anhydride (**53**), thiosemicarbazide (**54**) and various substituted benzaldehydes (**1**) in the presence of commercially available baker's yeast as catalyst in acetonitrile at room temperature (Figure 9.18). Under the same reaction conditions, synthesis of 2-[pyrazol-4-yl-methylene-hydrazono]-1,3-thiazolidin-4-one-5-yl-acetic acids (**57**) was also achieved by using 1,3-diaryl-pyrazole-4-carbaldehyde derivatives (**55**) instead of normal substituted benzaldehydes.

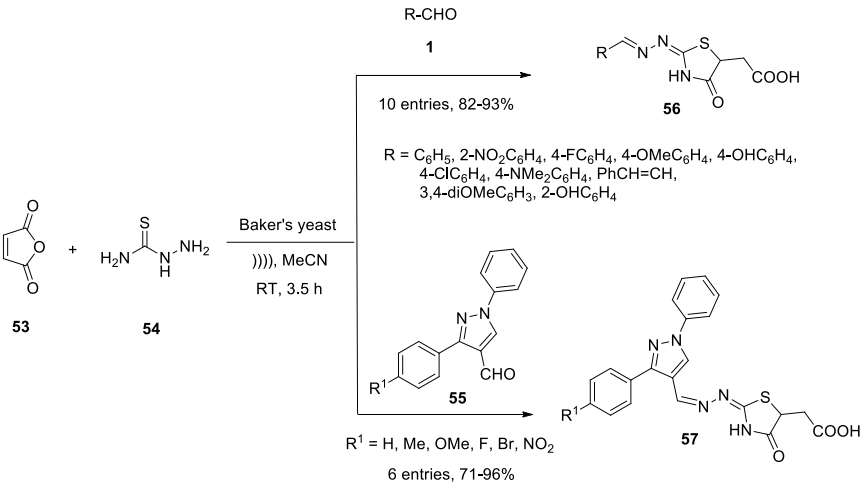


Figure 9.18: Baker's yeast catalyzed synthesis of 1,3-thiazolidin-4-one-5-acetic acid derivatives.

9.2.4.2 Synthesis of 2,3-disubstituted 1,4-benzothiazines

In 2011, Pratap *et al.* [71] reported a facile and ultrasound-assisted protocol for the efficient synthesis of 2,3-disubstituted 1,4-benzothiazines (**59**) from the reactions of 2-aminothiophenols (**58**) and 1,3-dicarbonyls (**5**) in methanol at ambient temperature (Figure 9.19). It was found that β-ketoesters afforded higher yields than the 1,3-diketones. It was proposed that the oxidative co-enzymes (NAD^+/FAD) produced by baker's yeast may take part in the conversion of 2-aminothiophenols (**58**) into the corresponding disulfides (**60**) (Figure 9.20).

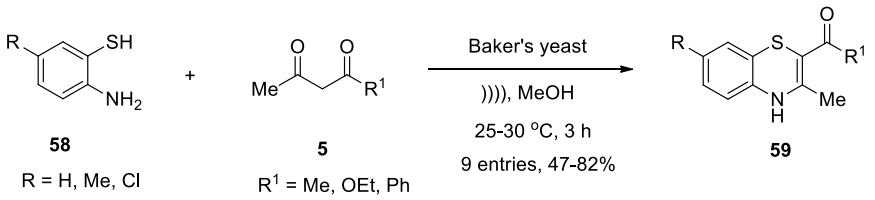


Figure 9.19: Baker's yeast catalyzed synthesis of 2,3-disubstituted 1,4-benzothiazines under ultrasonication.

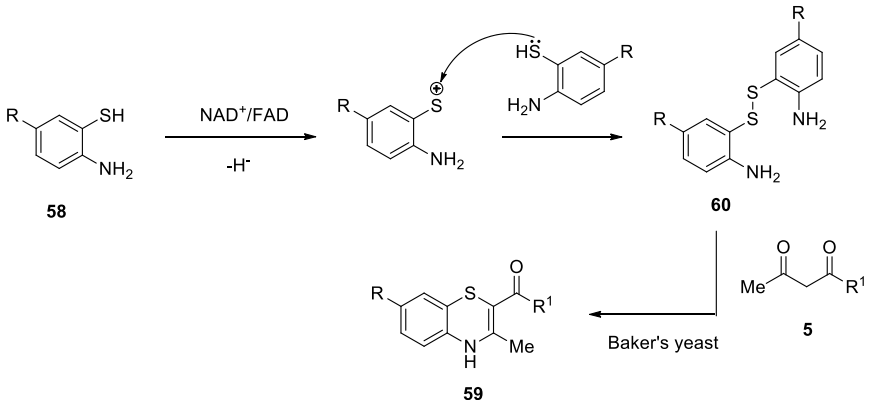
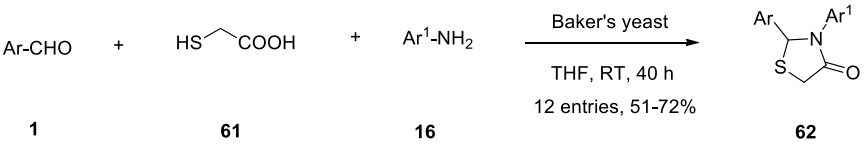


Figure 9.20: Plausible mechanism of baker's yeast catalyzed synthesis of 2,3-disubstituted 1,4-benzothiazines under ultrasonication.

9.2.4.3 Synthesis of 2,3-diaryl-4-thiazolidinones

Pratap *et al.* [72] developed another baker's yeast catalyzed facile protocol. Using this protocol they synthesized 2,3-diaryl-4-thiazolidinone derivatives (**62**) in good to excellent yields *via* one-pot three-component reactions of substituted benzaldehydes (**1**), thioglycolic acid (**61**) and aryl amines (**16**) in tetrahydrofuran at room

temperature (Figure 9.21). Aryl aldehydes with both electron withdrawing as well as donating substituent underwent smoothly and afforded the corresponding 2,3-diaryl-4-thiazolidinones (**62**) with moderate to good yields.



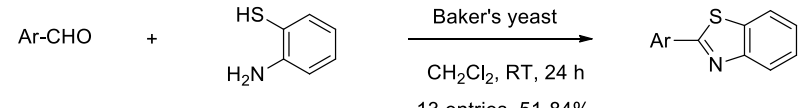
1 **61** **16** **62**

Ar = C_6H_5, 4-OHC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 3-$NO_2C_6H_4$
Ar^1 = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4

Figure 9.21: Baker's yeast catalyzed synthesis of 2,3-diaryl-4-thiazolidinone derivatives.

9.2.4.4 Synthesis of 2-arylbenzothiazoles

Baker's yeast was also found as an efficient biocatalyst for the synthesis of a series of 2-arylbenzothiazoles (**63**) from the reactions of aromatic aldehydes (**1**) and 2-aminothiophenols (**58**) in dichloromethane at room temperature (Figure 9.22) [73]. Aldehydes with both electron donating as well as withdrawing substituent afforded the corresponding 2-arylbenzothiazoles (**63**) with good to excellent yields. Heteroaryl aldehydes are also produced the desired products in good yields.



1 **58** **63**

Ar = C_6H_5, 4-$N(Me)_2C_6H_4$, 4-MeC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 2-OHC_6H_4, 3-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 2-pyridyl, 2-furyl

Figure 9.22: Baker's yeast catalyzed synthesis of 2-arylbenzothiazole derivatives.

9.2.4.5 Synthesis of thiazoles, imidazo[2,1-b][1,3,4]thiadiazoles, and [1,2,4] triazolo[3,4-b][1,3,4]thiadiazines

Along with *N*-heterocycles, Khillare *et al.* [56] synthesized various biologically promising *S*,*N*-heterocycles *via* the cyclocondensation of various nucleophiles with phenacyl chlorides (**28**) using baker's yeast as an efficient biocatalyst (Figure 9.23). Synthesis of 4-arylthiazol-2-amines (**68**) was carried out by the reactions of phenacyl chlorides (**28**) and thiourea (**64**) in the presence of a catalytic amount of baker's yeast in acetonitrile at room temperature. Reactions of phenacyl chlorides (**28**) and benzothioamide (**65**) afforded the corresponding 2,4-diarylthiazole derivatives (**69**) in excellent yields. Under the same optimized reactions conditions, synthesis of

2,6-diarylimidazo[2,1-*b*][1,3,4]thiadiazoles (**70**) was achieved by the reactions of phenacyl chlorides (**28**) and 5-phenyl-1,3,4-thiadiazol-2-amine (**66**). Reactions of 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (**67**) and phenacyl chlorides (**28**) generated the desired product 3,6-diaryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**71**) in excellent yields. Eco-friendly and mild protocol, use of biocatalyst, structural diversity, wide range of substrate scope are some of the notable advantages of this reported protocol.

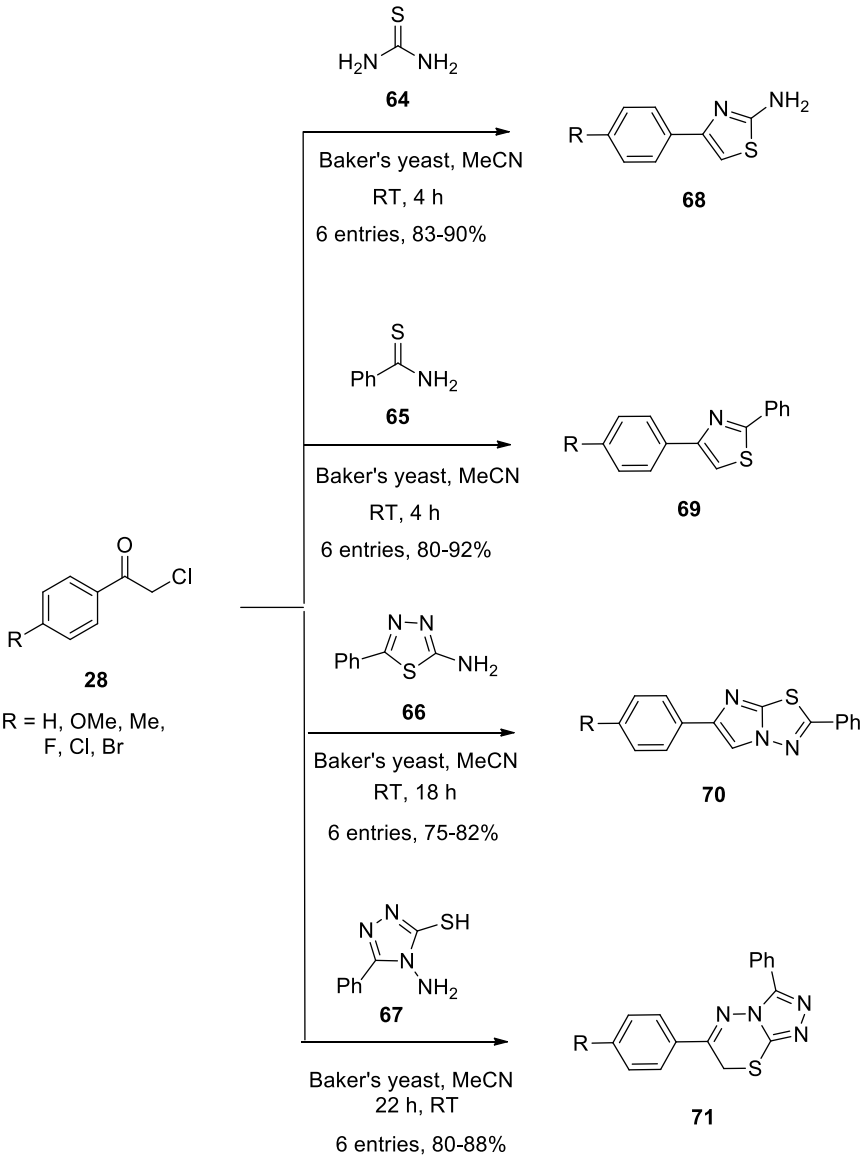


Figure 9.23: Baker's yeast catalyzed synthesis of thiazoles, imidazo[2,1-*b*][1,3,4]thiadiazoles and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines.

9.3 Baker's yeast catalyzed miscellaneous reactions

9.3.1 Reduction of carbonyl compounds

Yadav *et al.* [74] demonstrated baker's yeast catalyzed enantioselective reduction of α-azido acetophenones (**72**) to the corresponding (*R*)-(-)-2-azido-1-arylethanols (**73**) (Figure 9.24). At the initial stage of the reaction, yeast was fermented properly at room temperature by using phosphate buffer (pH 6.5) and sucrose solution. Tosa *et al.* [75] developed a simple and facile procedure for the quantative reduction of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes (**74**) to (10-alkyl-10*H*-phenothiazine-3-yl)methanols (**75**) by using catalytic amount of baker's yeast in ethanol at room temperature (Figure 9.25). They also observed that the baker's yeast catalyzed protocol is much more advantageous in terms of reaction times as well as product yields than the conventional $NaBH_4$ reduction process.

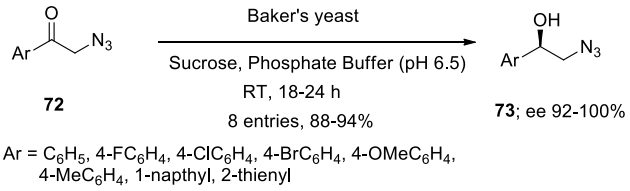


Figure 9.24: Baker's yeast catalyzed enantioselective reduction of α-azido acetophenones.

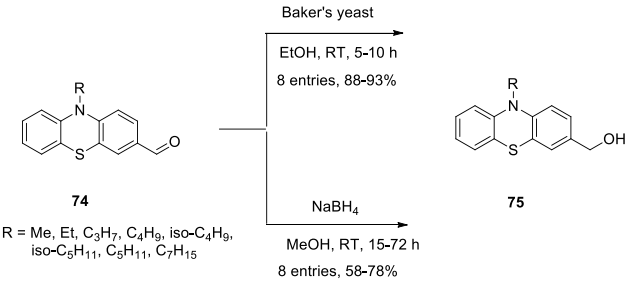
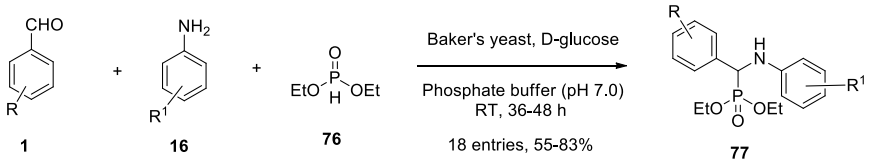


Figure 9.25: Baker's yeast catalyzed reduction of 10-alkyl-10*H*-phenothiazine3-carbaldehydes.

9.3.2 Synthesis of α-aminophosphonates

Bhattacharya and Mujahid [76] reported baker's yeast catalyzed one-pot three-component Strecker reactions of aldehydes (**1**), amines (**16**) and diethyl phosphite (**76**) which afforded the corresponding α-aminophosphonates (**77**) in moderate to good yields under solvent-free reaction conditions (Figure 9.26). Initially baker's yeast fermented properly at room temperature by stirring it overnight with phosphate buffer

(pH 7) and sucrose solution. Aldehydes with both electron donating as well as withdrawing substituent underwent efficiently and afforded the desired products in high yields.

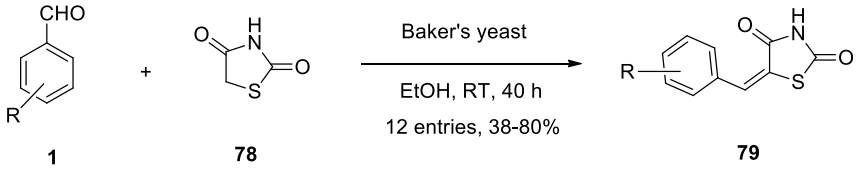


R = H, 4-OH, 4-OMe, 3-OH-4-OMe, 4-OH-3-OMe, 4-NO_2, 2-OH-3-OMe, 4-F, 4-Me, 2-OH, 4-OMe, 3-NO_2
R^1 = H, 2-OMe, 2-OH, 3-F

Figure 9.26: Baker's yeast catalyzed synthesis of α-aminophosphonates at room temperature.

9.3.3 Synthesis of 5-arylidene-2,4-thiazolidinediones

5-Arylidene-2,4-thiazolidinedione derivatives (**79**) are found to possess a wide range of biological activities including anti inflammatory [77], anticancer [78], tyrosine phosphate inhibitor [79], aldose reductase inhibitor [80], antihypertensive [81], and antifungal [82] activities. Pratap *et al.* [83] utilized baker's yeast as an efficient biocatalyst for the synthesis of 5-arylidene-2,4-thiazolidinediones from the reactions of substituted benzaldehydes (**1**) and thiazolidine-2,4-dione (**78**) in ethanol at room temperature (Figure 9.27).



R = H, 3-Cl, 2-Cl, 4-F, 4-Cl, 4-Br, 2-OH, 4-OCH_3, 4-OH, 4-$N(Me)_2$, 3,4-diOMe, 2-Cl, 4-F, 2,4-diCl, 4-Me

Figure 9.27: Baker's yeast catalyzed synthesis of 5-arylidene-2,4-thiazolidinediones at room temperature.

9.3.4 Synthesis of 3,3′-(arylmethylene)bis(4-hydroxy-2H-chromen-2-one) derivatives

Saha and Pal [68] showed that prefermented baker's yeast is an efficient catalyst for the synthesis of 3,3′-(arylmethylene)*bis*(4-hydroxy-2*H*-chromen-2-ones) (**80**) from the reactions of one equivalent of aromatic aldehydes (**1**) and two equivalents of

4-hydroxycoumarin (**47**) in aqueous medium at room temperature (Figure 9.28). Mild reaction protocol, environmental friendliness, use of water as solvent, short reaction times, and excellent yields are some of the salient features of this protocol.

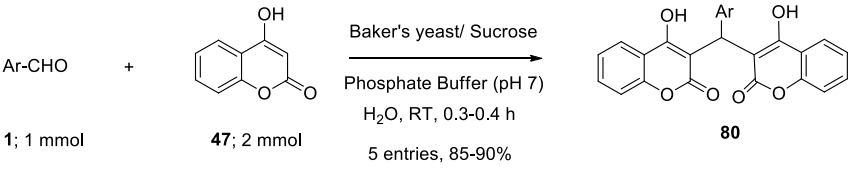


Figure 9.28: Baker's yeast catalyzed synthesis of 3,3′-(arylmethylene)*bis*(4-hydroxy-2*H*-chromen-2-one) derivatives at room temperature.

9.3.5 Synthesis of bis(indolyl)methanes

Baker's yeast was fermented by 12 h continuous stirring with D-glucose in the presence of phosphate buffer (pH 7) at room temperature. Using this prefermented baker's yeast as catalyst, a number of *bis*(indolyl)methane derivatives (**82**) were synthesized from the pseudo three-component reactions of one equivalent of aldehydes (**1**) and two equivalents of indole (**81**) in aqueous medium at room temperature (Figure 9.29) [59].

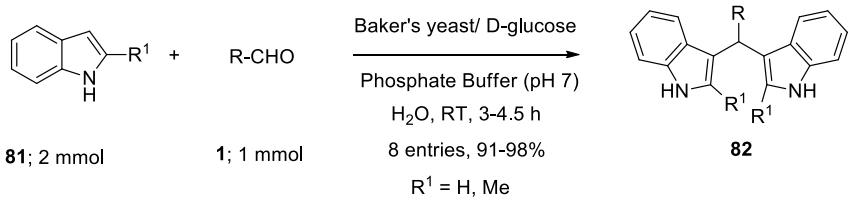


Figure 9.29: Baker's yeast catalyzed synthesis of *bis*(indolyl)methanes at room temperature.

9.4 Conclusions

During last two decades, baker's yeast (*S. cerevisiae*) has gained huge attention as a mild, commercially available, low cost, stereoselective and environmentally benign biocatalyst for various organic transformations. Baker's yeast was capable to catalyze the reactions that were previously reported either by using metal catalysts or under harsh conditions. Various heterocyclic scaffolds were synthesized by using baker's yeast as the catalyst. On many occasions, prefermented baker's yeast showed better catalytic activities than the freshly added catalyst. It may be due to the catalytic

efficiency of the enzymes present in it increases under prefermented conditions. Baker's yeast catalyzed reactions can be carried out in water. Though, in general, the baker's yeast catalyzed reactions require longer times but the mild reaction conditions, ecofriendliness and high stereoselectivity are some of the notable advantages of those protocols.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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10 Bronsted acidic surfactants: efficient organocatalysts for diverse organic transformations

Abstract: Organic transformations using efficient, atom-economical, cost-effective and environmentally benign strategies for the construction of diversified molecules have attracted synthetic chemists worldwide in recent years. These processes often minimize the waste production and avoid the use of hazardous flammable organic solvents. Among various green protocols, the procedures using surfactant-based catalytic systems have received a considerable attention in organic synthesis. In this context, Bronsted acidic surfactants have emerged as efficient catalysts for various C–C, C–O, C–N and C–S bond forming reactions. Many of these reactions occur in water, as Bronsted acidic surfactants have a unique ability of creating hydrophobic pocket through micelle formation in aqueous medium and the substrate molecules react efficiently to afford the targeted products in good yields. In the past, Bronsted acidic surfactant combined catalysts successfully displayed their potential to accelerate the reaction rates of diverse organic transformations. This chapter presents a complete overview on Bronsted acidic surfactants catalyzed organic reactions to construct a variety of aromatic and heteroaromatic molecular frameworks.

Keywords: aqueous synthesis; Bronsted acidic surfactants; catalysts; DBSA; heterocycles.

10.1 Introduction

Organic synthesis plays a key role in the construction of organic entities ranging from bioactive molecules to strategically important building blocks with several synthetic and material applications. In fact, many traditional methods for the synthesis of these important classes of molecules involve toxic reagents and highly flammable organic solvents. As a result, these processes often generate hazardous waste materials and by-products which adversely affect the sustainable development of environment.

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Hence, green synthetic methodologies are gaining a continuous attraction of chemists worldwide for the preparation of diverse molecular frameworks using environmentally benign reaction conditions. In the past decades, several green synthetic strategies have been developed to carry out a variety of chemical reactions by employing either green preferred solvents/media including water, ethanol and ionic liquids or solvent-free surroundings [1]. Moreover, eco-friendly protocols avoid the use of toxic reagents and solvents and thus, produce negligible toxic waste during the course of reaction. Among the environmentally benign solvents, water is a most preferred green solvent as it is readily available, inexpensive, non-toxic, and it triggers various organic transformations by activating the functional groups of substrate molecules through hydrogen bonding [2]. Besides, one of the major disadvantages associated using water as a reaction medium is its inability to dissolve certain organic substrates/reagents due to the high dielectric constant that becomes a reason for sluggish reactions. However, the literature search revealed that the rate of reactions can be significantly accelerated by adding surfactant-type catalysts in the aqueous media [3]. As the surfactant combined catalysts have both hydrophobic and hydrophilic groups present in their chemical structures, they form micellar dispersion when come in contact with water (Figure 10.1) and facilitate the reaction to afford desired products in high yields.

Based on the charges possessed by the molecular chain, the surfactant-combined catalysts can be categorized into four major classes such as anionic, cationic, zwitterionic and non-ionic surfactants [3]. They have been utilized commonly as catalysts for carrying out a number of organic transformations and one-pot multicomponent reactions in water. To this end, surfactant-type Bronsted acidic catalysts have also been found to expedite reaction dynamics *via* the formation of micelles in water where reactions proceeded smoothly through an aggregation of hydrophilic polar heads and hydrophobic chains. Interestingly, the long alkyl chains present in various Bronsted acids form a hydrophobic core which accelerates the reaction between hydrophobic substrates under aqueous conditions. Hence, a wide variety of organic transformations have been reported in the past by utilizing various Bronsted acidic surfactant catalysts including *p*-octylbenzenesulfonic acid (OBSA; **1**), *p*-dodecylbenzenesulfonic acid (DBSA; **2**), lauric acid (**3**) dodecylsulfonic acid (DSA; **4**), perfluorooctanesulfonic acid (**5**) (Figure 10.2). Among these Bronsted acidic surfactants, DBSA has emerged as an efficient and versatile acidic catalyst for catalyzing numerous organic transformations.

These surfactant combined Bronsted acidic catalysts are broadly used to carry out various water-sensitive reactions. Generally, they form a colloidal dispersion with hydrophobic substrates *via* a micelle formation and allow the reaction in the hydrophobic

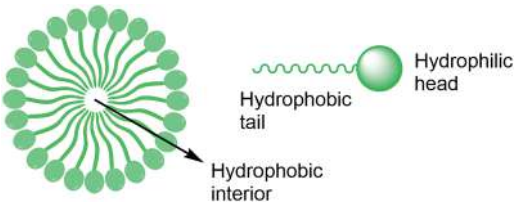

Figure 10.1: A graphic representation of micelles formation after surfactants interact with water.

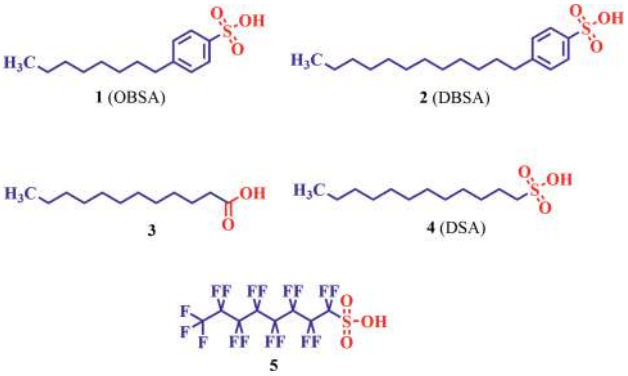

Figure 10.2: The representative molecular structures of some Bronsted acidic surfactant catalysts.

pocket under aqueous conditions as depicted in Figure 10.3. During the dehydration step, the hydrophobic core of the catalyst immediately removes the water outside the micelle and force the reaction equilibrium toward forward direction to afford the imine product in high yield.

10.2 Bronsted acidic surfactant-catalyzed organic reactions

Bronsted acidic surfactant combined catalysts have been successfully employed to accelerate the rates of a variety of organic transformations to generate diverse organic compounds in the past decades as discussed in the following sections.

10.2.1 Acetylation of alcohols

Acetylation reaction using acetic anhydride is a most common way to protect alcohols by acetyl group. To this end, DBSA has been effectively used as a stable Bronsted acid

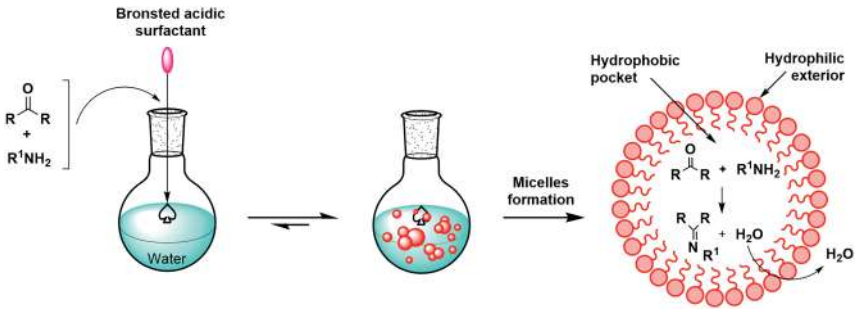

Figure 10.3: Bronsted acidic surfactant catalyzed synthesis of imine in water.

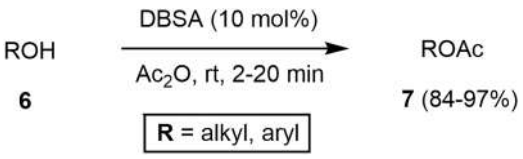

Figure 10.4: DBSA-promoted acetylation of alcohols.

surfactant combined catalyst for the acetylation of alcohols (**6**) to produce esters (**7**) with acetic anhydride under solvent-free conditions at ambient temperature (Figure 10.4). It was observed that the reaction in case of primary alcohols proceeded at a faster rate as compared with the secondary and tertiary alcohols. Apart from this, selective acetylation of the primary alcohols was also achieved even in the presence of secondary or tertiary alcohols by using this methodology. In comparison to other acidic catalysts such as *p*-toluenesulfonic acid (PTSA), DBSA was found to be a best suited catalyst for this conversion due to its surfactant combined acidic characteristics and provides corresponding products (**7**) in short reaction times [4].

10.2.2 Aldol reaction

Cheng and co-workers have reported a highly effective chiral catalytic system (**8**; Figure 10.5) which selectively catalyzes the synthesis of (S)-2-((R)-hydroxy(aryl) methyl)cyclohexan-1-ones (**11**) through an aldol reaction in water (Figure 10.6). A variety of chiral organocatalysts were synthesized *in situ* by coupling chiral amines with DBSA in aqueous medium to control stereoselective desymmetrization of a prochiral cyclohexanones (**9**) during the aldol condensation with substituted benzaldehydes (**10**). Among various chiral amine-Bronsted acid salts, diethyl-(pyrrolidin-2-yl)methyl-ammonium salt (**8**) with DBSA as a non-covalent anchor (Figure 10.5) has shown better stereoselectivity. It is interesting to note that catalysts obtained after the combination of chiral amines with a series of other Bronsted acids including PTSA provided the product in lower yields with poor stereoselectivity as compared with the DBSA [5].

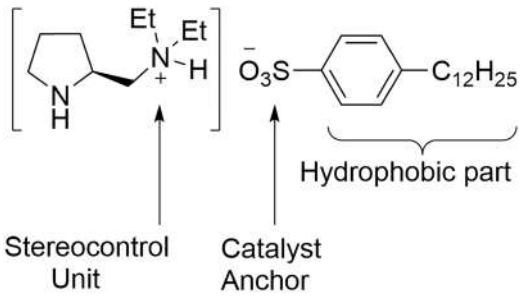

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Figure 10.5: The structure of diethyl-(pyrrolidin-2-yl)methyl-ammonium salt-based chiral catalyst.

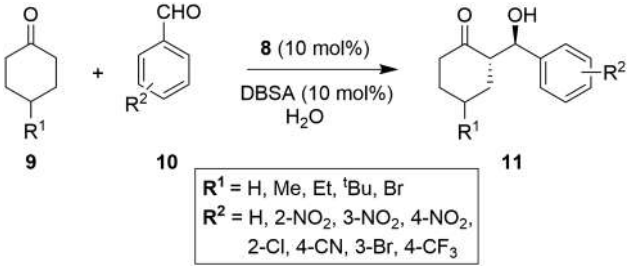


Figure 10.6: Synthesis of (S)-2-((R)-hydroxy(aryl)methyl)cyclohexan-1-ones.

10.2.3 Biginelli reaction

Biginelli reaction is a strategically important one-pot three-component reaction of ethylacetoacetate derivatives (**12**), aldehydes (**13**) and urea or thiourea (**14**) to construct biologically relevant 3,4-dihydropyrimidin-2-ones (**15**) which display diverse pharmaceutical profiles such as antibacterial, antitumor, anti-inflammatory and antiviral agents [6]. According to the literature reports, Biginelli reaction was catalyzed using various acidic catalysts to prepare a variety of 3,4-dihydropyrimidin-2-one analogues. Bigdeli et al. have reported the synthesis of 3,4-dihydropyrimidinones (**15**) by the reaction of 1,3-diketones (**12**), aromatic aldehydes (**13**) and urea (**14**) in the presence of 20 mol% DBSA as a Bronsted acidic catalyst under aqueous and neat conditions [7] as depicted in Figure 10.7. Similarly, Konwar and co-workers have carried out the synthesis of a library of 3,4-dihydropyrimidinones (**15**) in good to excellent yields under the influence of 10 mol% DSA in water at ambient temperature (Figure 10.7) using 1,3-diketones (**12**), aldehydes (**13**) and urea or thiourea (**14**) as starting materials [8].

10.2.4 Condensation-cyclization reactions

Thorough literature survey revealed that the rates of a wide range of condensation-cyclization reactions were successfully accelerated using surfactant combined

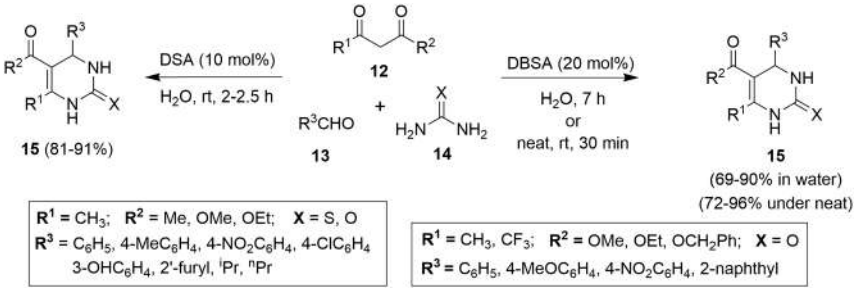


Figure 10.7: Ambient temperature synthesis of 3,4-dihydropyrimidin-2-ones in water.

Bronsted acidic catalysts to construct diverse aromatic and fused heterocycles. The synthetic methodologies for these molecules are discussed in the following subsections.

10.2.4.1 Synthesis of thiazolidinones

Thiazolidinones exhibit a broad range of pharmacological activities and emerged as important scaffolds in medicinal chemistry [9]. In addition, some thiazolidinone derivatives are proved to be important substrates for the synthesis of various functional and pharmaceutical molecules such as monofluoro-β-lactam [10], pyrazolothiazole [11], and polymethine cyanine dyes [12]. Considering the importance of these molecules in diverse areas, a series of 2,3-disubstituted-4-thiazolidinones were synthesized by Nath et al. through a one-pot three-component environmentally benign synthetic strategy which uses DBSA as an efficient catalyst in an aqueous medium [13]. The aromatic aldehydes (**16**), aliphatic or aromatic primary amines (**17**) and mercaptoacetic acid were reacted in water containing 10 mol% DBSA at room temperature and provided the desired thiazolidinone products (**18**) in good yields (Figure 10.8).

Additionally, spiro[indole-thiazolidinones] have also been synthesized by following various methodologies involving the reaction of amines, isatins and mercaptoacetic acid under different set of reaction conditions [14–17]. However, some of the reported methods suffer with multiple disadvantages such as longer reaction times, high reaction temperatures, use of flammable organic solvents, tedious workup, use of expensive catalysts and harsh reaction conditions. To overcome these complications, Nath's group have designed the synthesis of a series of spiro[indoline-3,2′-thiazolidinone] analogues (**22**) through a DBSA-catalyzed sequential reaction of isatin derivatives (**19**) with primary amines (**20**) and mercaptoacetic acid in aqueous medium at room temperature [18].

First, the isatin derivatives (**19**) were allowed to react with primary aromatic amines (**20**) in water in the presence of DBSA as a Bronsted acid catalyst for 18 h at room temperature to obtain the corresponding Schiff base intermediate (**21**). Further, mercaptoacetic acid was added to the same pot which afforded the desired spiro[indoline-

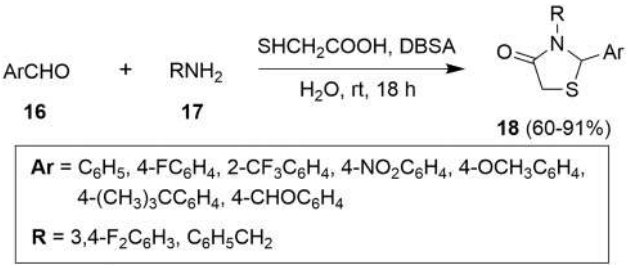


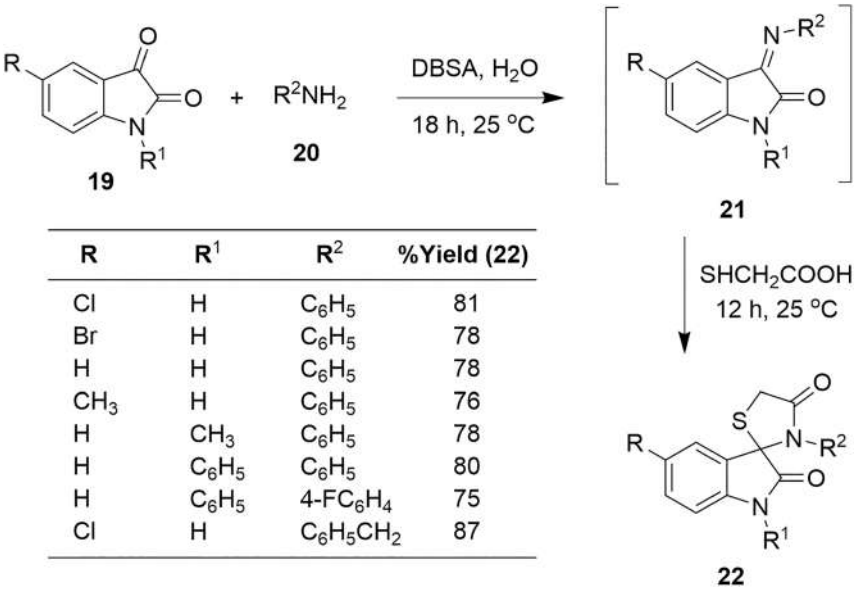
Figure 10.8: DBSA-catalyzed one-pot three-component synthesis of 4-thiazolidinones.

3,2′-thiazolidinone] products (**22**) in appreciable yields (Figure 10.9). According to proposed mechanism, the reaction proceeded with the formation of Schiff's base intermediate after the reaction of an amine with isatin. This imine intermediate forms an iminium cation under the influence of DBSA. Later, this iminium cation intermediate undergoes intramolecular cyclization on reaction with mercaptoacetic acid to afford spiro[indoline-3,2′-thiazolidinone] product. In comparison to many other methods, this protocol was found to be simple, energy efficient, environment-friendly and economical.

10.2.4.2 Synthesis of indazoles

The indazole analogues such as spiro-cyclopropyl indolinones [19] and axitinib [20] have shown a wide range of biological applications such as antitumor, antiangiogenesis and multikinase inhibitor properties. Previously, indazoles were synthesized using Suzuki-Miyaura cross-coupling and palladium-catalyzed Heck reactions [21]. Nevertheless, transition metal-free synthesis of indazoles has attracted the interest of researchers. Many of these methods have been found to be substrates specific and less versatile [22–25].

To this end, Ren et al. have reported a synthesis of *trans*-3-alkenyl-2-pyrrolidine-2*H*-indazoles (**24**) in moderate to excellent yields through an intramolecular cyclization of allylic triazenylaryl alcohols (**23**) under mild conditions using DBSA as a Bronsted acid catalyst in aqueous medium (Figure 10.10) [26].



R	R^1	R^2	%Yield (22)
Cl	H	C_6H_5	81
Br	H	C_6H_5	78
H	H	C_6H_5	78
CH_3	H	C_6H_5	76
H	CH_3	C_6H_5	78
H	C_6H_5	C_6H_5	80
H	C_6H_5	4-FC_6H_4	75
Cl	H	$C_6H_5CH_2$	87

Figure 10.9: Aqueous phase synthesis of spiro[indoline-3,2′-thiazolidinones].

Figure 10.10: DBSA-accelerated synthesis of indazole analogues in water.

10.2.4.3 Synthesis of benzimidazoles

Benzimidazole substituted at N-1 or C-2 positions have attracted the interest of many researchers around the globe due to their wide range of biological importance and pharmacological applications [27]. Additionally, 2-substituted benzimidazole nucleus is present as a structural part of several clinical medicines such as Esomeprazole (anti-ulcerative agent) [28], and Albendazole [29], that is used to treat parasitic diseases. Besides, benzimidazoles are essential precursors in several organic transformations [30, 31] and also present as key components of various functional materials [32]. These fused heterocycles have been prepared through various chemical reactions including the condensation of an *o*-diaminoarenes with aldehydes [33], reductive cyclization of *o*-nitroanilines with aldehydes, cascade reaction between *o*-haloanilines and amidine hydrochlorides and hydroformylation reaction of *N*-alkenylphenylenediamines [34]. However, most of the procedures are restricted to use hazardous and flammable organic solvents during the course of reaction and workup. By following a green methodology, Banerjee et al. synthesized the 2-substituted benzimidazole derivatives (**27**) by the reaction of *o*-phenylenediamine (**25**) with a series of aldehydes (**26**) using DBSA as an effective Bronsted acidic surfactant combined catalyst in presence of iodine as a co-catalyst in water at room temperature [35]. However, a small amount of 1,2-disubstituted benzimidazoles (**28**) were also obtained as by-products (Figure 10.11). The proposed mechanistic pathway for the formation of mono- and disubstituted

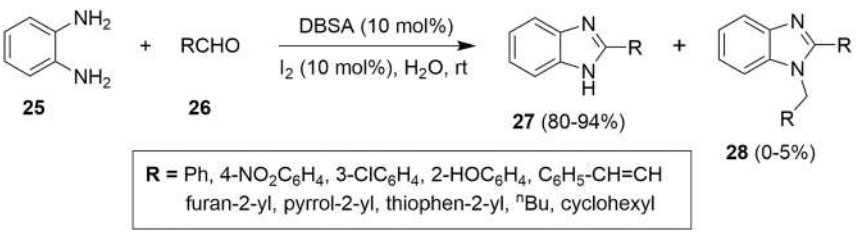


Figure 10.11: DBSA-I_2 catalyzed synthesis of benzimidazoles.

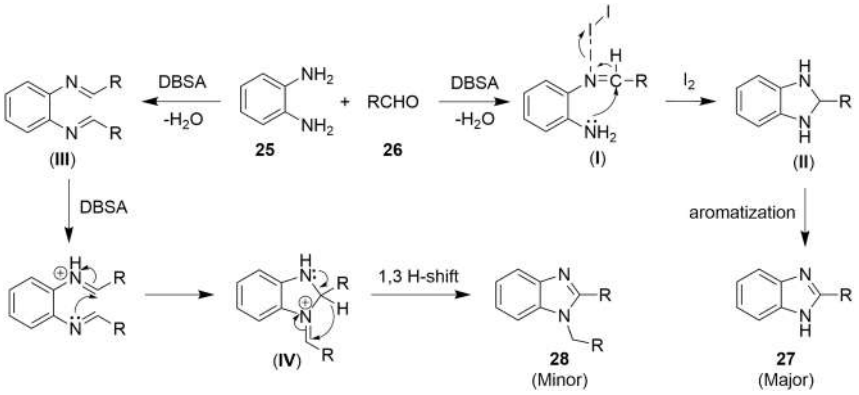


Figure 10.12: Proposed mechanism for the formation of benzimidazoles (**27** and **28**).

benzimidazoles is depicted in Figure 10.12. Interestingly, the methodology was found to be efficient and versatile to afford 2-substituted benzimidazoles in good to excellent yields by employing diverse aliphatic, aromatic and heterocyclic aldehydes and *o*-phenylenediamine as starting materials.

The scope of this methodology was further examined by reacting *o*-phenylenediamine (**25**) with 2-formylchromone (**29**) under standardized reaction conditions which provided a macrocycle, 2,3:9,10-dibenzo-6,13-disalicyloyl-1,8-dihydro-1,4,8,11-tetraaza [14]annulene (**30**) as a sole product instead of the expected benzimidazole derivative (Figure 10.13).

10.2.4.4 Synthesis of dihydropyrano[2,3-*c*]pyrazoles

One-pot three-component synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazoles (**33a-e**) was reported by Li and co-workers [36] by reacting aromatic aldehydes (**16**), 3-methyl-1-phenyl-2-pyrazolin-5-one (**31**) and malononitrile (**32**) in aqueous medium using *p*-dodecylbenzenesulfonic acid as an efficient catalyst (Figure 10.14).

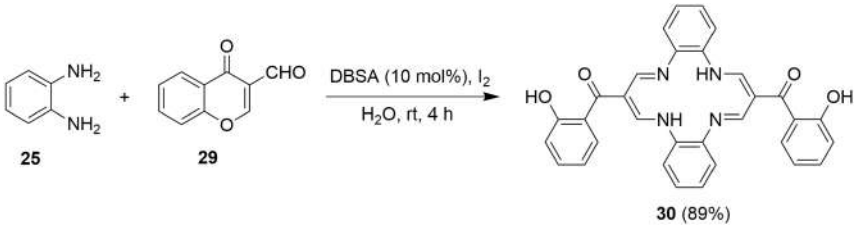


Figure 10.13: Synthesis of 2,3:9,10-dibenzo-6,13-disalicyloyl-1,8-dihydro-1,4,8,11-tetraaza[14] annulene.

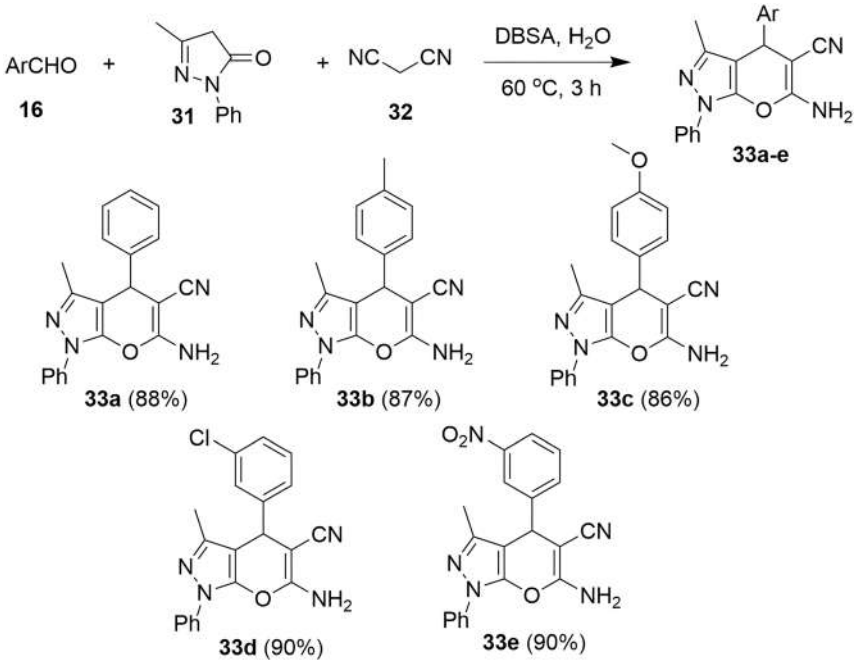


Figure 10.14: Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*] pyrazoles.

Later, Das et al. have reported the synthesis of tricyclo-4-spiropyrano[2,3-*c*]pyrazoles (**37**) through a one-pot three-component reaction of pyrazolones (**36**), cyclohexane-1,3-diones and indan-1,2,3-trione using DBSA as a catalyst in water at 90 °C (Figure 10.15). First, a mixture of hydrazine hydrate (**34**) and ethylacetoacetate (**35**) was stirred in water in presence of DBSA to form the corresponding pyrazolone (**36**) followed by the addition of cyclohexan-1,3-diones and indan-1,2,3-trione to form the desired products (**37**) in appreciable yields [37].

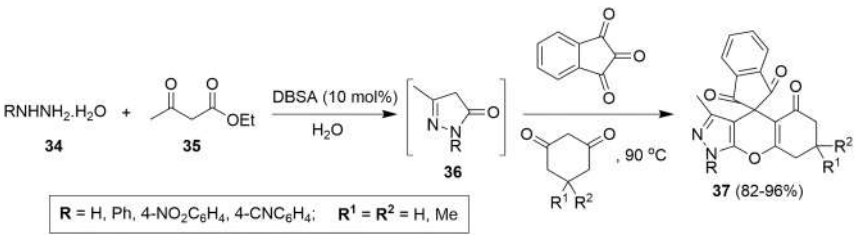


Figure 10.15: Synthesis of tricyclo-4-spiropyrano[2,3-*c*]pyrazoles.

10.2.4.5 Synthesis of quinoxalines

Quinoxalines are one of the important classes of nitrogen-containing heterocycles which exhibit a wide range of biological activities such as anticancer, anti-inflammatory, antibacterial and antiviral agents [38]. Hence, a large number of synthetic protocols have been developed in the past several decades to prepare various quinoxaline analogues through a condensation reaction of *o*-phenylenediamines with benzils using a wide range of catalysts such as ceric ammonium nitrate [39], $Yb(OTf)_3$ [40], $CuSO_4.5H_2O$ [41], Zn[(L)proline] in AcOH [42], molecular iodine in DMSO [43], ionic liquids [44] and montmorillonite K-10 [45]. Besides these methods, an alternative eco-friendly synthesis of quinoxalines using inexpensive and non-toxic Bronsted acidic surfactant combined catalyst was reported by Peiravi and co-workers [46]. The methodology involves a reaction of benzil derivatives (**38**) with *o*-phenylenediamines (**39**) using DBSA as a catalyst in water at room temperature to construct the corresponding 2,3-diarylquinoxalines (**40**) in high yields (Figure 10.16).

10.2.4.6 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

2,3-Dihydroquinazolin-4(1*H*)-one analogues have demonstrated their significance in a wide range of biological activities such as antifungal [47], antibacterial [48], antitumor [49], antidiabetic [50] and HIV-1 reverse transcriptase inhibitors [51]. Therefore, efforts have been made to synthesize these molecules through various traditional and eco-friendly synthetic methodologies. 2,3-Dihydroquinazolin-4(1*H*)-one derivatives (**43**) were synthesized by Chen and co-workers [52] by using an environmentally benign synthetic protocol which involves a one-pot three-component reaction of amines (**20**), isatoic anhydride (**41**) and aromatic aldehydes (**42**) in the presence of a catalytic amount of DBSA under aqueous medium and ultrasound irradiation at 40–42 °C which afforded the desired 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**43**) in 83–90% yields within 2 h (Figure 10.17). According to proposed mechanism, the driving force of cascade reaction is a protonation of carbonyl functionality of isatoic anhydride by DBSA which enhances the nucleophilic attack of amine at the carbonyl group. In addition, DBSA also activates the carbonyl group of aldehyde to accelerate the rate of condensation-cyclization under ultrasound irradiation to afford the desired products.

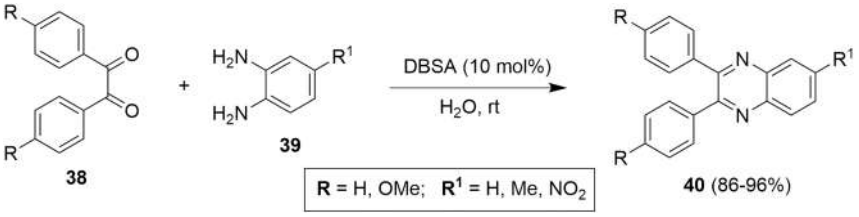


Figure 10.16: DBSA-catalyzed synthesis of quinoxalines in water.

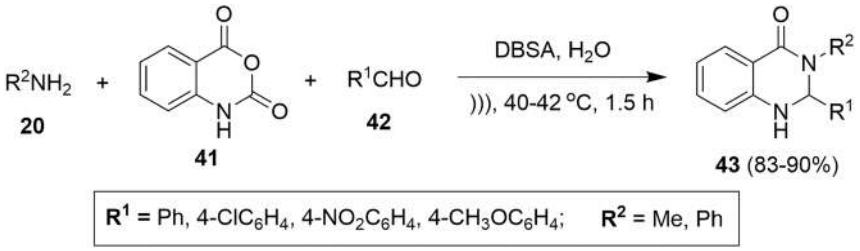


Figure 10.17: Eco-friendly synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under ultrasound irradiation.

10.2.4.7 Synthesis of 1,8-dioxo-decahydroacridines

1,8-Dioxo-decahydroacridine derivatives having 1,4-dihydropyridine scaffold have attracted the interests of synthetic chemists worldwide due to their medicinal applications. The appropriately functionalized 1,8-dioxo-decahydroacridines have shown their ability to treat various cardiovascular diseases, such as angina pectoris [53] and hypertension [54]. In the past, several conventional synthetic methods were developed to construct the 1,4-dihydropyridines. These methods generally involve the use of flammable organic solvents [55] which are detrimental to the environment. In view of this, Li et al. have developed a one-pot three-component environment-friendly synthesis of 1,8-dioxo-decahydroacridines (**46**) by reacting aromatic aldehydes (**44**), dimedone (**45**) and *p*-toluidine in water containing a catalytic amount of *p*-dodecylbenezenesulfonic acid [56]. The reported one-pot methodology was found to be efficient to provide the title products (**46**) in 79–92% yields (Figure 10.18). On the other hand, Wang and co-workers synthesized an imidazolium based Bronsted acidic organocatalyst with surfactant properties [57] to catalyze above cascade reaction for the preparation of a series of 1,8-dioxo-decahydroacridines (**46**) in decent yields (Figure 10.18). Later, Sriram and co-workers reported a microwave-assisted reaction of aromatic aldehydes (**44**), dimedone (**45**) and isonicotinic hydrazide in water containing DBSA as an acidic catalyst to construct various isoniazid analogues (**47**) in 65–94% yields (Figure 10.18). In addition, the synthesized molecules were examined for their anti-TB activity against *Mycobecterium tuberculosis* [58]. Some of these isoniazid analogues exhibited significant efficacy with MIC values in the range of 0.17–1.52 μM concentration. The biological results are quite interesting and may be useful for the development of novel acridine-based anti-TB agents.

10.2.4.8 Synthesis of xanthenes

Xanthenes are biologically active heterocyclic motifs with several applications including anticancer [59], antibacterial [60], antiviral [61], anti-proliferative [62], anti-inflammatory [63] properties and photosensitizers in photodynamic therapy

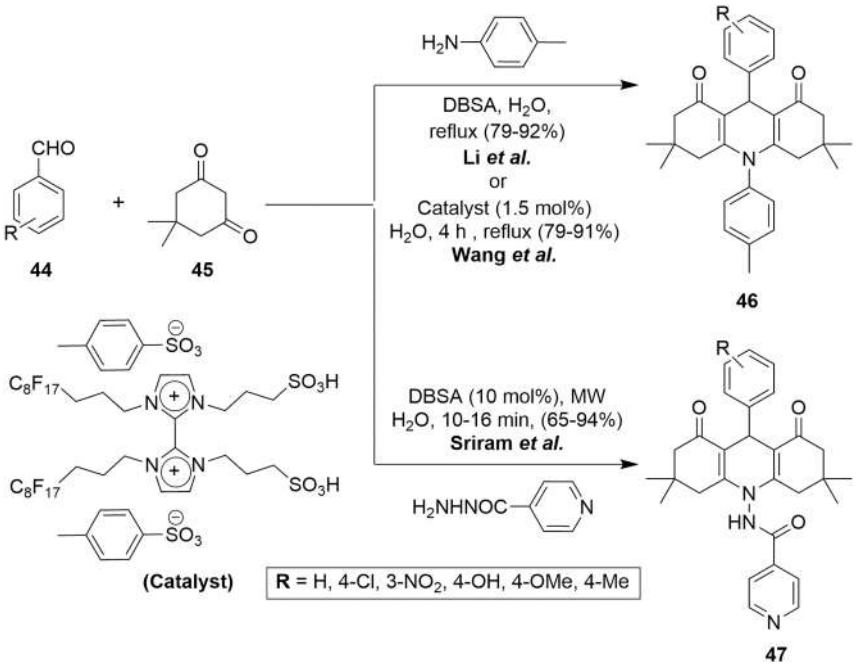


Figure 10.18: Synthesis of 1,8-dioxo-decahydroacridines.

applications [64]. Additionally, a wide range of xanthene-based compounds have been used as fluorescent dyes [65], in laser technology [66] and pH-sensitive fluorescent materials [67]. Xanthenes can be synthesized by various methods including the reaction of aryloxymagnesium halides with triethylorthoformate [68], condensation cyclization of 2-tetralone with salicyldehyde [69] or intramolecular trapping of benzynes with phenols [70]. However, there are several drawbacks associated with these methods such as long reaction times, use of excess reagents or catalyst, use of hazardous solvents or harsh conditions. Hence, Nath et al. developed an environment-friendly synthesis of xanthenes using Bronsted acidic surfactant as an efficient catalyst under solvent-free conditions [71]. In particular, the synthesis of 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes (**49**) was reported by following a one-pot condensation-cyclization of a wide range of aliphatic or aromatic aldehydes (**26**) with *β*-naphthol (**48**) in the presence of a catalytic amount of DBSA under microwave irradiation (Figure 10.19). Interestingly, the desired products were obtained in excellent yields in a very short period of time.

Besides, Li et al. have synthesized various xanthene derivatives (**50**) using DBSA as an acidic catalyst under ultrasound irradiation [72]. In this methodology, 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthenes (**50**) were prepared by the reaction of aromatic aldehydes (**16**) with dimedone (**45**) in water containing 10 mol%

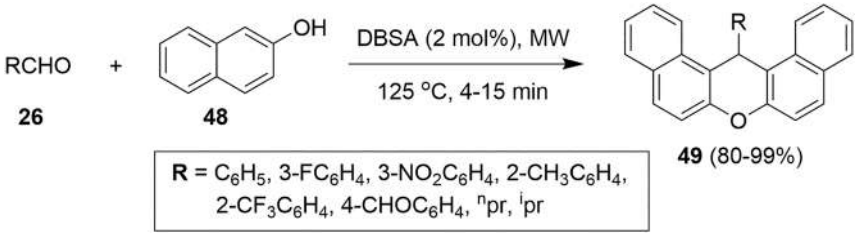
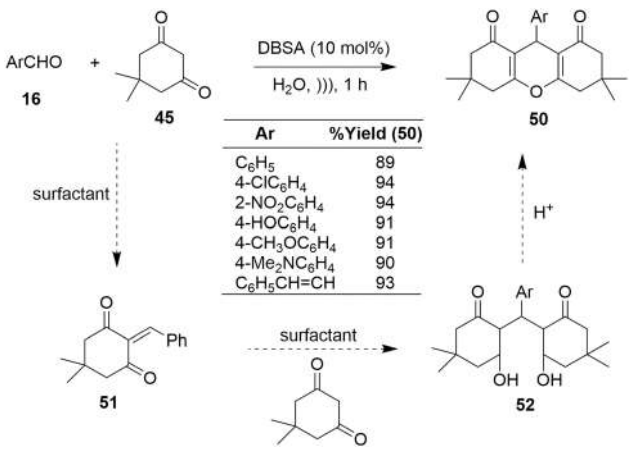


Figure 10.19: Synthesis of 14-substituted-14*H*-dibenzo[*a*,*j*]xanthenes.

DBSA under ultrasonic conditions (Figure 10.20). Among the various catalyst examined including PTSA, SDS + PTSA, DBSA, lauric acid and the quaternary ammonium salts (tetrabutylammonium bromide TBAB, cetyltrimethylammonium bromide CTAB), DBSA was found to be superior in catalyzing the reaction to provide the desired products (**50**) in maximum yields. Even the lauric acid containing long alkyl chain along with a carboxylic group was found to be less effective as compared with the DBSA and provided the xanthene products in poor yields. The high catalytic efficiency of DBSA may be attributed to its highly acidic sulfonyl group in the formation of xanthenes.

In the case of quaternary ammonium salts as catalysts, the reaction stops after the formation of dihydroxy intermediates (**52**). Later, it has been proved that the formation of the desired xanthenes (**50**) requires an acidic medium to accelerate the intramolecular cyclization of intermediate (**52**) followed by dehydration in the final step of the reaction. Similarly, a series of phenyl-bridged bis-xanthenes (**55**) were also synthesized by refluxing 1,4-diformylbenzene (**53**) and cyclohexane-1,3-diones (**54**) in



Ar	%Yield (50)
C_6H_5	89
4-ClC_6H_4	94
2-$NO_2C_6H_4$	94
4-HOC_6H_4	91
4-$CH_3OC_6H_4$	91
4-$Me_2NC_6H_4$	90
$C_6H_5CH{=}CH$	93

Figure 10.20: Synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthenes.

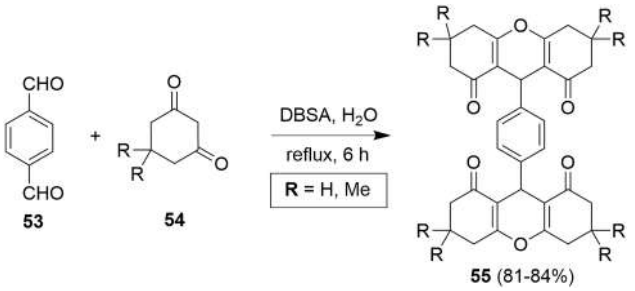


Figure 10.21: DBSA-catalyzed synthesis of phenyl-bridged bis-xanthenes.

water using DBSA as a Bronsted acid catalyst [73] (Figure 10.21). This method has demonstrated several advantages such as high yields, environment-friendly conditions and simple workup procedures.

Song and co-workers developed an efficient methodology to synthesize 12-phenyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**56**) by a three-component condensation reaction of *β*-naphthol, substituted benzaldehydes and cyclohexane-1,3-diones (**54**; Figure 10.22). The reaction was carried out in presence of catalytic amount of DBSA in water at 40–42 °C under ultrasound irradiation (40 kHz) for 80 min which provided the products (**56**) in 76–93% isolated yields. Interestingly, when the reaction was performed in other protic solvents such as ethanol and methanol, the formation of product was not observed. However, the products (**56**) were obtained in 64–85% yields after performing the reactions in absence of ultrasonic condition [74].

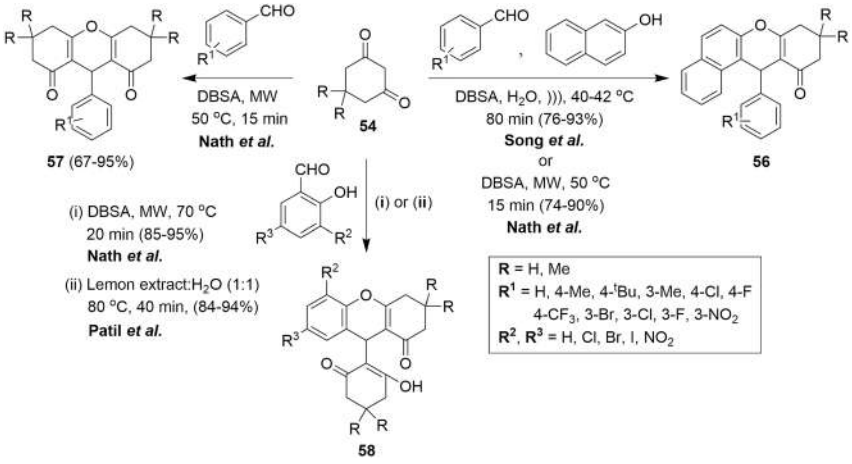


Figure 10.22: Synthetic routes to various xanthene scaffolds.

On the other hand, Nath et al. employed the DBSA as an efficient catalyst under microwave conditions [75] to construct the 12-phenyl-8,9,10,12-tetrahydrobenzo[*a*] xanthen-11-ones (**56**) in excellent yields within 15 min (Figure 10.22). In addition, the reaction of benzaldehyde derivatives and cyclohexa-1,3-diones (**54**) under same reaction conditions produced 9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-diones (**57**) in good yields. Interestingly, the methodology was further extended to construct 9-substituted-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones (**58**) by the reaction of dimedone with salicylaldehyde derivatives.

Alternatively, Patil and co-workers have constructed 9-substituted-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones (**58**) in good yields by the reaction of dimedone with salicylaldehydes using lemon-extract as an efficient Bronsted acidic biosurfactant catalyst in water (Figure 10.22). It is interesting to note that the use of a biodegradable catalyst under aqueous conditions makes this process environmentally benign [76].

10.2.4.9 Synthesis of benzodiazepines

The benzodiazepine-based drugs have been found as potent inhibitors of HIV-1 reverse transcriptase enzyme [77]. Therefore, the efforts toward synthesis of benzodiazepine analogues gained considerable attention in recent years. In this context, Konwar and co-workers have reported a synthetic strategy for the synthesis of 1,5-benzodiazepines by employing DSA as an efficient Bronsted acidic surfactant catalyst [8]. Under standardized conditions, reactions of *o*-phenylenediamine (**25**) with ketones (**59**) were smoothly carried out in the presence of 10 mol% DSA in water at ambient temperature and provided 1,5-benzodiazepine products (**60**) in 86–90% yields (Figure 10.23).

10.2.5 Cycloaddition reactions

The green chemical synthesis of isoxazolidine heterocycles was reported by Chattopadhyay and co-workers in an aqueous medium using DBSA as a Bronsted acidic surfactant catalyst [78]. The aldoximes (**61**) were treated with ethyl acrylate using 5 mol% DBSA in water under heating conditions to afford the *N*-alkylated nitrones (**62**), which later undergo cycloaddition reaction with maleimide to form maleimide-fused

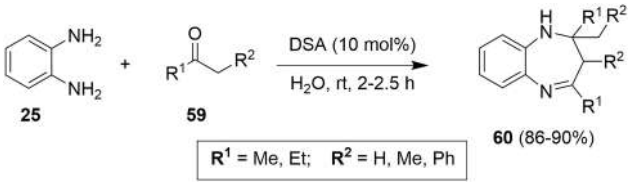


Figure 10.23: DSA-catalyzed aqueous phase synthesis of 1,5-benzodiazepines.

isoxazolidine derivatives (**63**) in moderate yields (Figure 10.24). To evaluate the catalytic efficiency of DBSA, an experiment was performed by using a non-surfactant Bronsted acidic catalyst such as PTSA which was failed to catalyze the reaction under same reaction conditions. However, the combination of PTSA and CTAB provided the products in poor yields. These results clearly suggested that an acidic catalyst with surfactant properties such as DBSA is highly required to catalyze the formation of maleimide-fused isoxazolidine derivatives (**63**).

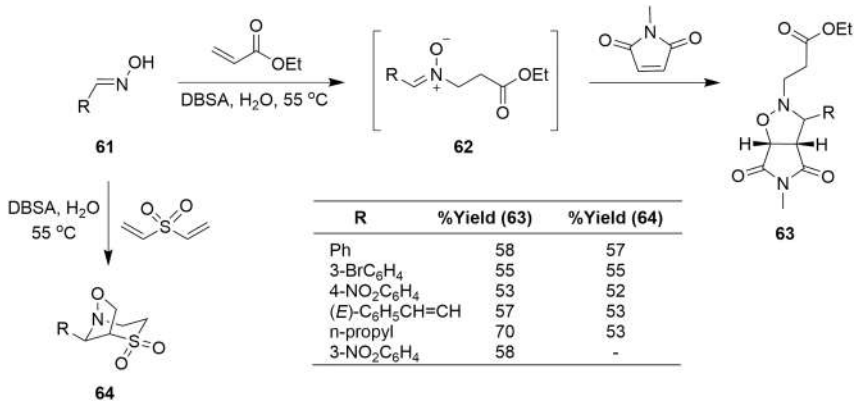
Interestingly, an intramolecular-cycloaddition reaction of aldoximes (**61**) and divinylsulfone under optimized conditions produced bicyclic products (**64**) in moderate yields (Figure 10.24).

10.2.6 Cyclotrimerization of acetophenones

Nath et al. have reported a green synthetic methodology to synthesize 1,3,5-triarylbenzenes (**66**) by a solvent-free cyclotrimerization of acetophenones (**65**) in the presence of DBSA as an efficient Bronsted acidic surfactant combined catalyst at 130 °C [79]. The desired symmetrical 1,3,5-triarylbenzenes (**66**) were obtained in good to excellent yields (Figure 10.25).

10.2.7 Dimerization of 2-amino-*meso*-tetraphenylporphyrins

Recently, Nath et al. employed DBSA as an efficient Bronsted acidic catalyst for the dimerization of nickel(II) 2-amino-5,10,15,20-tetraphenylporphyrins (**67**) to construct the nickel(II) β-pyrazine-fused *meso*-tetraphenyldiporphyrins (**68**). The nickel(II) 2-amino-5,10,15,20-tetraphenylporphyrins (**67**) were heated in 1,4-dioxane in presence of 20 mol% DBSA for an hour to afford the desired products (**68**) in good yields



R	%Yield (63)	%Yield (64)
Ph	58	57
3-BrC_6H_4	55	55
4-$NO_2C_6H_4$	53	52
(*E*)-C_6H_5CH=CH	57	53
n-propyl	70	53
3-$NO_2C_6H_4$	58	-

Figure 10.24: Synthesis of isoxazolidines and 7-oxa-4-thia-1-azabicyclo[3.2.1]octane-4,4-dioxides.

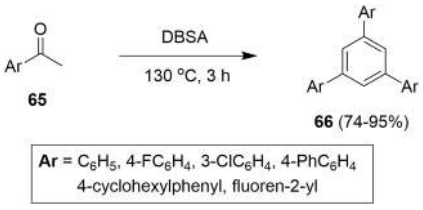


Figure 10.25: Eco-friendly synthesis of 1,3,5-triarylbenzenes under solvent free conditions.

(Figure 10.26). Interestingly, these molecules demonstrated encouraging photophysical properties due to their extended electronic conjugation [80].

10.2.8 Esterification reactions

Often the synthetic operational steps in the esterification process are found to be in equilibrium. Therefore, it is necessary to remove the water molecules from the reaction mixture in order to shift the equilibrium toward forward direction. It was reported for the first time to perform the esterification of alcohols in aqueous medium using DBSA as a surfactant combined acidic catalyst by Kobayashi and co-workers [81]. The esterification reaction of various carboxylic acids (**69**) with alcohols (**70**) was performed in an aqueous medium by employing DBSA as a Bronsted acidic surfactant catalyst in water at 40 °C to afford corresponding esters (**71**) in good yields (Figure 10.27). It is proposed that the organic reactants such as carboxylic acids (**69**) and alcohols (**70**) form aggregates after interaction with surfactant catalyst to produce droplets in water and generate hydrophobic interior in the medium. The reaction occurs inside this hydrophobic interior and water molecules generated during the course of reaction are removed from the cavity due to the resistance created by the long hydrocarbon chain of DBSA. Thus, this phenomenon shifts the equilibrium toward forward direction.

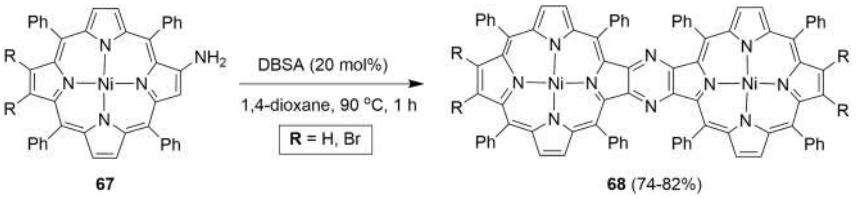


Figure 10.26: DBSA-catalyzed synthesis of nickel(II) β-pyrazine-fused *meso*-tetraphenyldiporphyrins.

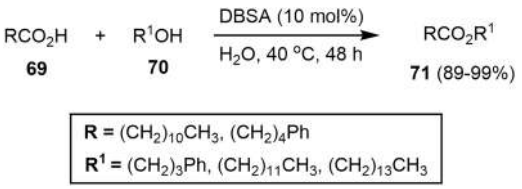


Figure 10.27: DBSA-catalyzed esterification of carboxylic acids under aqueous conditions.

10.2.9 Formylation of alcohols

The formylation of various alcohol derivatives (**6**) have been carried out using ethyl formate as an acylating reagent in presence of DBSA as an efficient and stable Bronsted acid surfactant combined catalyst. The reaction of alcohols (**6**) with ethyl formate was carried out under neat conditions at room temperature which afforded aldehydes (**26**) in moderate to good yields (Figure 10.28). In addition, the catalyst was recycled up to three catalytic cycles without any significant loss in its efficiency [4].

10.2.10 Fridel-Crafts alkylation

Kobayashi and co-workers have reported the Friedel-Crafts type alkylation of heteroatom-centered nucleophile such as 1-methylindole (**72**) with benzyl alcohol derivatives using DBSA as a Bronsted acidic surfactant catalyst in water [82]. Initially, the reaction was performed using 1-methylindole (**72**) and diarylmethanol as substrates in presence of 10 mol% DBSA as a catalyst in water at 80 °C which provided the 3-diarylmethyl-1-methylindole (**73**) as the alkylated products in good isolated yields (Figure 10.29). Later, this protocol was successfully extended for the alkylation of diverse aromatic and heteroaromatic compounds using a wide range of benzyl alcohol analogues to obtain the corresponding products. The common acidic catalysts such as acetic acid, trifluoroacetic acid, PTSA and triflic acid were found to be ineffective to catalyze the reaction. However, the reaction proceeded smoothly to provide three-substituted indole derivatives in good yields by using DBSA as an acidic catalyst which signifies that strong Bronsted acid with surfactant property is necessary to accelerate the rate of reaction.

Later, Chen's group performed an alkylation of 1-methylindole (**72**) by using 1,3-diphenylallylmethyl alcohol in presence of 1 mol% calix[6]arenesulfonic acid-based surfactant-catalyst in water at ambient temperature generates 3-(1,3-diphenylallyl)-1-methyl-1*H*-indole (**74**) in excellent yield (Figure 10.29). Moreover, the catalyst can be easily recovered from the reaction mixture through simple centrifugation and utilized directly up to seven catalytic cycles without any significant loss of its efficiency [83].

This methodology found its application in stereoselective dehydrative C-glycosylation of 1-hydroxy sugars (**75**) in water [84] (Figure 10.30). A Friedel-Craft type nucleophilic substitution reaction of 1-hydroxy-D-ribofuranose with aromatic and hetero-aromatic architectures (**76**) provided the C-nucleosides (**77**) with very good β-selectivity.

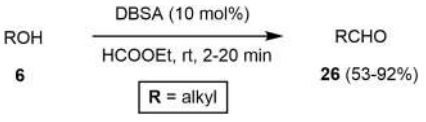


Figure 10.28: DBSA-promoted formylation of alcohols to synthesize aldehydes.

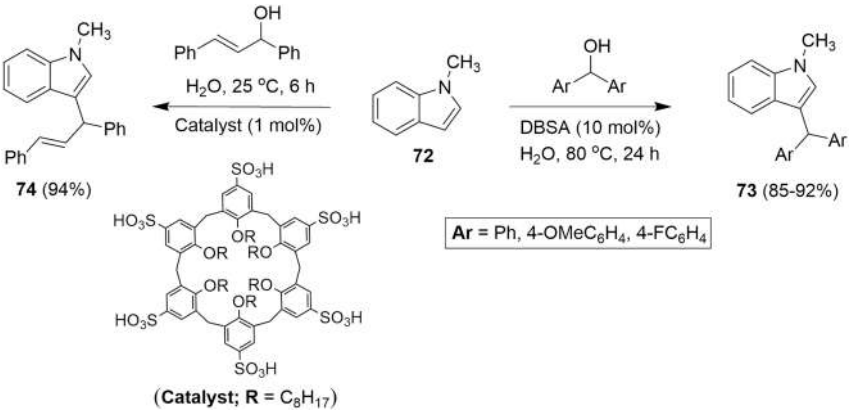


Figure 10.29: Synthesis of 3-diarylmethyl- and 3-(1,3-diphenylallyl)-1-methylindoles.

Recently, Liao et al. have reported the Friedel-Craft alkylation of a cyclic ketene dithioacetal (**78**) with diphenylmethanol (**79**) involving DBSA as a catalyst in water under reflux conditions to form the 3-[1,3]dithiolan-2-ylidene-4,4-diphenyl-butan-2-one (**80**) in excellent yield (Figure 10.31) [85]. Interestingly, the yield of desired product (**80**) was decreased when reactions were performed at lower temperatures. The proposed mechanism revealed that DBSA transfers a proton to the alcohol substrate and facilitates the generation of a carbocation intermediate after dehydration. This electron deficient reactive intermediate under a nucleophilic attack of cyclic ketene dithioacetal at its α-carbon ultimately affords the target compound (**80**).

10.2.11 Kabachnik-Fields reaction

Kabachnik-Fields reaction is known to synthesize α-aminoalkylphosphonates by a three-component reaction of a carbonyl compound, an amine and trialkylphosphite under the influence of acid catalysts. In literature, several acidic catalysts such as

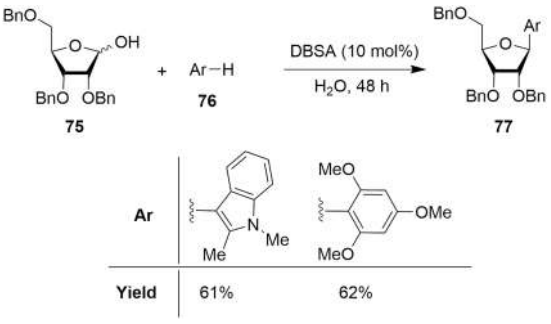


Figure 10.30: Synthesis of 1-aryl- and 1-heteroaryl-D-ribofuranose derivatives.

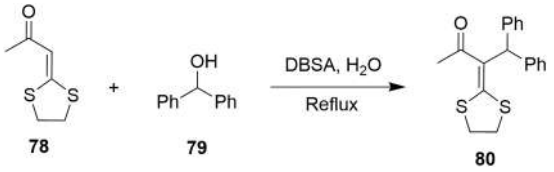


Figure 10.31: Synthesis of alkylated cyclic ketene dithioacetal.

$Mg(ClO_4)_2$, $Zn(ClO_4)_2$, $BF_3.OEt_2$ and $SnCl_4$ [86, 87] have been reported for the synthesis of *α*-aminoalkylphosphonates. However, these catalysts have some limitations due to their unstability and moisture sensitivity.

To this end, Alapour and co-workers have successfully synthesized *α*-aminomethylphosphonates (**83**) at room temperature using a one-pot three-component reaction [88] of amines (**20**), aldehydes (**81**) and trimethylphosphite (**82**) using DBSA as a catalyst in water (Figure 10.32). The proposed mechanism suggested that DBSA plays a key role in the formation of Schiff's base and subsequent electrophilic iminium ion by protonation which expedite the nucleophilic attack of trimethylphosphite (**82**) to form the desired product (**83**) very efficiently.

10.2.12 Knoevenagel-Michael addition reaction

Knoevenagel condensation is the reaction of carbonyl compounds with substrates having active methylene group under basic conditions. Whereas, Michael addition reaction involves the addition of a nucleophile to an *α*,*β*-unsaturated carbonyl system. These two reactions have been utilized to construct oxygen heterocycles by reacting carbonyl compounds with 4-hydroxycoumarin in the presence of acidic catalysts. In view of this, a tandem Knoevenagel-reductive Michael addition reaction was carried out for the synthesis of 3-(aryl)methyl-4-hydroxycoumarins (**86**) (Figure 10.33). The reaction of aromatic or heteroaromatic aldehydes (**26**) and 4-hydroxycoumarin (**84**) in water under one-pot ultrasonic conditions using Hantzsch 1,4-dihydropyridine as a hydride donor and DBSA as a Bronsted acid surfactant-combined catalyst provided the corresponding products (**86**) in 27–88% yields within 1.5 h [89].

Later, a synthesis of a series of bis(4-hydroxycoumarin) derivatives (**87**) were also achieved through conventional as well as microwave heating conditions in the

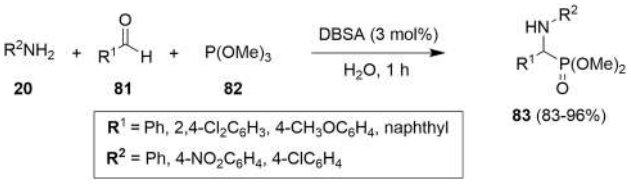


Figure 10.32: Synthesis of *α*-aminomethylphosphonates.

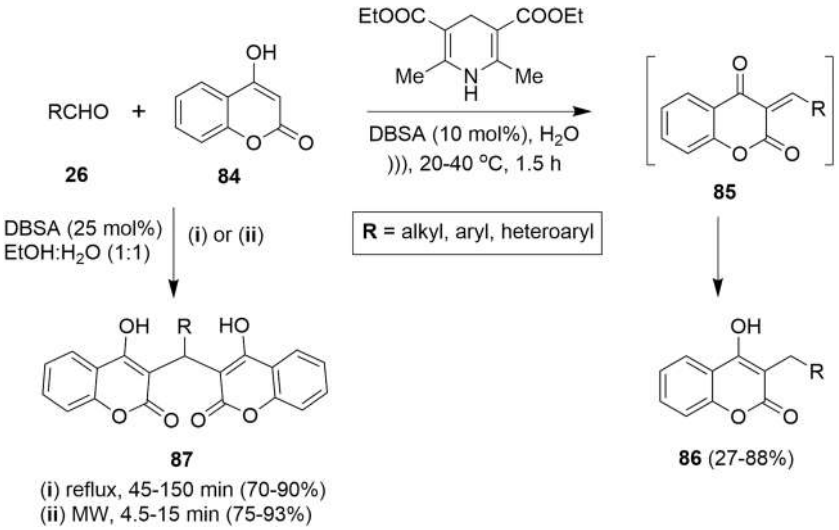
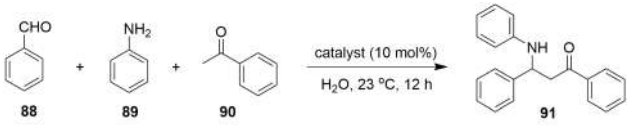


Figure 10.33: Synthesis of 4-hydroxycoumarin derivatives through Knoevenagel-reductive Michael addition.

presence of DBSA as a catalyst in ethanol-water mixture at reflux temperature (Figure 10.33) [90]. Though, conventional and microwave methods afforded the desired products in good yields but in the case of microwave heating the products were obtained in significantly less time (4–15 min) as compared to the conventional methods (45–150 min).

10.2.13 Mannich reaction

Mannich-type reactions are beneficial to synthesize β-aminocarbonyl compounds (**91**) [91, 92], by a three-component reaction of benzaldehyde (**88**), aniline (**89**) and acetophenone (**90**). Mannich reaction in organic solvents have substrate limitations like enolization of aliphatic aldehydes and often facilitates undesired side reactions [91]. To overcome these complications, DBSA was used as a surfactant catalyst in water which forms emulsion with insoluble organic reactants and thereby increases the rate of reaction (Figure 10.34). Additionally, this reaction was also carried out in methanol and dichloromethane containing a catalytic amount of DBSA, but the results were not fruitful due to the lower yield (<10%) of desired product (**91**). The efficiency of this reaction depends solely upon the hydrophobic interactions between substrate molecules and catalyst under aqueous environment. However, these interactions are found to be weak in organic solvents such as methanol and dichloromethane and resulted a lower yield of product [91]. Further, PTSA was completely failed to catalyze the reaction probably due to the absence of long alkyl chain, required for providing a hydrophobic



Catalyst	DBSA	$Sc(O_3SOC_{12}H_{25})_3$	PTSA	SDS	PTSA + SDS
%Yield	69	54	0	5	56

Figure 10.34: Three-component Mannich-type reaction to form β-aminoketone (**91**) under aqueous conditions.

surrounding to the substrate molecules. The formation of desired product was observed with modest yield when PTSA was used along with sodium dodecyl sulfate (SDS) under same reaction conditions. Probably, SDS helps to form a colloidal dispersion with the reactants, and PTSA catalyze the reaction by activating the carbonyl group of aldehydes and ketones.

A three-component Mannich-type reaction using aldehydes (**26**), *o*-anisidine (**92**) and silyl enolates (**93**) has been carried out in water in the presence of Bronsted acidic surfactant catalyst to form a various β-aminocarbonyl compounds (Figure 10.35). A variety of aromatic and aliphatic aldehydes (**26**) were made to react with *o*-anisidine (**92**) and substituted silyl enolates (**93**) in aqueous medium containing a catalytic amount of DBSA to give the corresponding β-aminocarbonyl derivatives (**94**) in good yields [93]. It is interesting to note that the formation of aldol and deamination products was not observed when ketone, ester and thioester-based silyl enolates were used in the reaction.

By considering the biological applications including anti-flammatory, antitumor, leishmanicidal, molluscicidal and antifungal activities of quinone embedded molecules [94], Greco et al. reported a one-pot synthesis of aminonapthoquinones (**98a-d**) in 56–85% isolated yields through a Mannich-type condensation of lawsone (**95**), aromatic aldehydes (**96a-d**) and 4-nitroaniline (**97**) in water using DBSA as an acidic catalyst (Figure 10.36). For this transformation, DBSA was found to be a superior acid catalyst over other catalytic systems such as Tween 80® and PTSA/SDS which either afforded the desired products in poor yields or failed to provide any desired product [95].

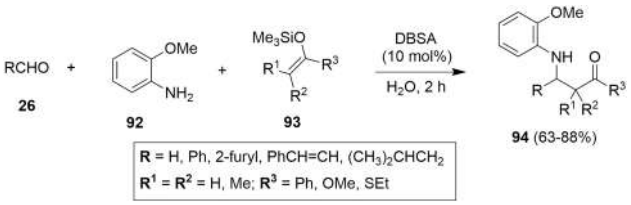


Figure 10.35: Mannich-type condensation to form β-aminoketones using silyl enolates as substrates.

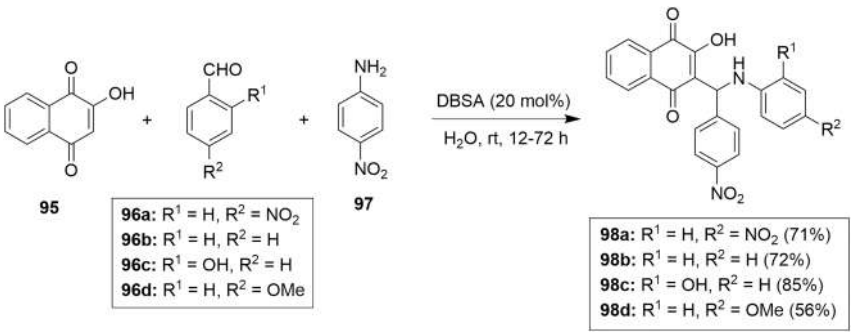


Figure 10.36: DBSA-catalyzed synthesis of aminonapthoquinones.

10.2.14 Pictet-Spengler reaction

Pictet-Spengler reaction of β-arylethyl carbamate (**99**) with aliphatic aldehydes (**100**) has also been performed in aqueous medium using perfluorooctanesulfonic acid (PFOSA) as a Bronsted acid-surfactant combined catalyst [96] at ambient temperature to construct the *N*-(methoxycarbonyl)-6,7-dimethoxy-1-alkyl-1,2,3,4-tetrahydroisoquinolines (**101**) in excellent yields (Figure 10.37). Initially, the reaction was carried out by employing mineral acids such as sulfuric and hydrochloric acids as catalyst but all the efforts were unsuccessful to provide any expected product. Further, various Bronsted acidic catalysts such as PTSA, trifluoracetic acid and trifluoromethanesulfonic acid have also been employed to catalyze the Pictet-Spengler reaction in organic media [97, 98] but in majority of these reactions, no product formation was observed. However, poor yields (~27%) of the desired products were obtained when the reactions were carried out in the presence of DBSA as a catalyst. Interestingly, when PFOSA was used with an additive such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), the yields of products (**101**) were increased up to 97%. In fact, PFOSA interacts with the substrate molecules to generate hydrophobic surroundings in water which get further reinforced by the presence of HFIP to eliminate water from reaction mixture very efficiently and affords the compounds (**101**) in high yields.

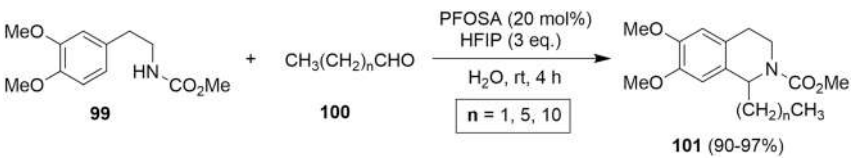


Figure 10.37: Synthesis of methyl *N*-(methoxycarbonyl)-6,7-dimethoxy-1-alkyl-1,2,3,4-tetrahydroisoquinolines.

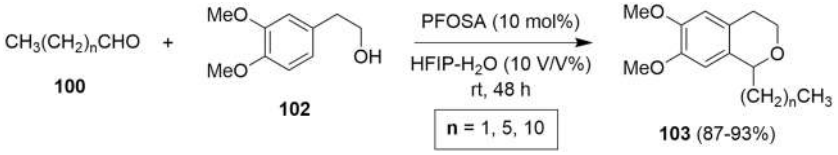


Figure 10.38: Synthesis of 1-alkyl-6,7-dimethoxyisochromanes.

Prompted from the synthesis of tetrahydroisoquinolines (**101**), the oxa-Pictet-Spengler reaction has been performed [96] by using *β*-arylethyl alcohol (**102**) as a substitute for the *β*-arylethyl carbamate (**99**) to construct 1-alkyl-6,7-dimethoxyisochromanes (**103**) under the similar reaction conditions (Figure 10.38). Interestingly, the PFOSA and HFIP combination worked well to catalyze the reaction in aqueous medium which provided the products (**103**) in 87–93% yields.

Considering the biological profiles of pyrrolo- and indolo[1,2-*a*]quinoxaline molecules as anti-proliferative [99], anticancer [100] and antimalarials [101], Nath et al. developed an eco-friendly Pictet-Spengler reaction of 1-(2-aminophenyl)pyrrole or 1-(2-aminophenyl)indole (**104**) with a wide range of aldehydes, acetophenones or isatins in ethanol at ambient temperature using the Bronsted acidic catalyst (DBSA) to construct a series of pyrrolo- and indolo[1,2-*a*]quinoxalines (**105**), dihydropyrrolo[1,2-*a*]quinoxalines (**106**), and spiro[indoline-3,4′-pyrrolo/indolo[1,2-*a*]quinoxalin]-2-ones (**107**), respectively (Figure 10.39). The synthetic strategy has been found to be advantageous and provided the products (**105–107**) in good yields using mild conditions over a very short span of time [102].

Later, Nath's group successfully extended the modified Pictet-Spengler reaction methodology to incorporate pyrrolo- and indolo[1,2-*a*]quinoxaline frameworks on porphyrin periphery [103]. Diverse copper(II) *β*-substituted pyrrolo- and indolo[1,2-*a*]quinoxalinoporphyrins (**109**) were constructed by the reaction of copper (II) *β*-formyl-5,10,15,20-tetraarylporphyrins (**108**) with 1-(2-aminophenyl)pyrrole or 1-(2-aminophenyl)-3-methylindole (**104**) in 1,4-dioxane containing a catalytic amount of DBSA at 25–40 °C followed by *in situ* oxidation by using aqueous potassium permanganate at room temperature (Figure 10.39). The synthesized porphyrinoids (**109**) showed the significant bathochromic shifts in their electronic absorption spectra as compared with their precursor molecules due to the extended π-conjugation. Hence, these compounds may have potential to be used as phototherapeutic agents in photodynamic therapy applications.

The same group has also carried out the Pictet-Spengler reaction on *β*-functionalized porphyrinic system using DBSA as an efficient catalyst. The synthetic methodology was developed for the first time to construct novel π-extended *β*,*β*′-fused nickel(II) pyrrolo[1,2-*a*]pyrazinoporphyrins (**111**) in moderate to good yields by the reaction of nickel(II) 2-amino-3-(pyrrol-1-yl)-5,10,15,20-tetraphenylporphyrin (**110**) with an aliphatic, aromatic or heterocyclic aldehydes using 1,4-dioxane as a solvent containing 10 mol% of DBSA at room temperature (Figure 10.40). The plausible

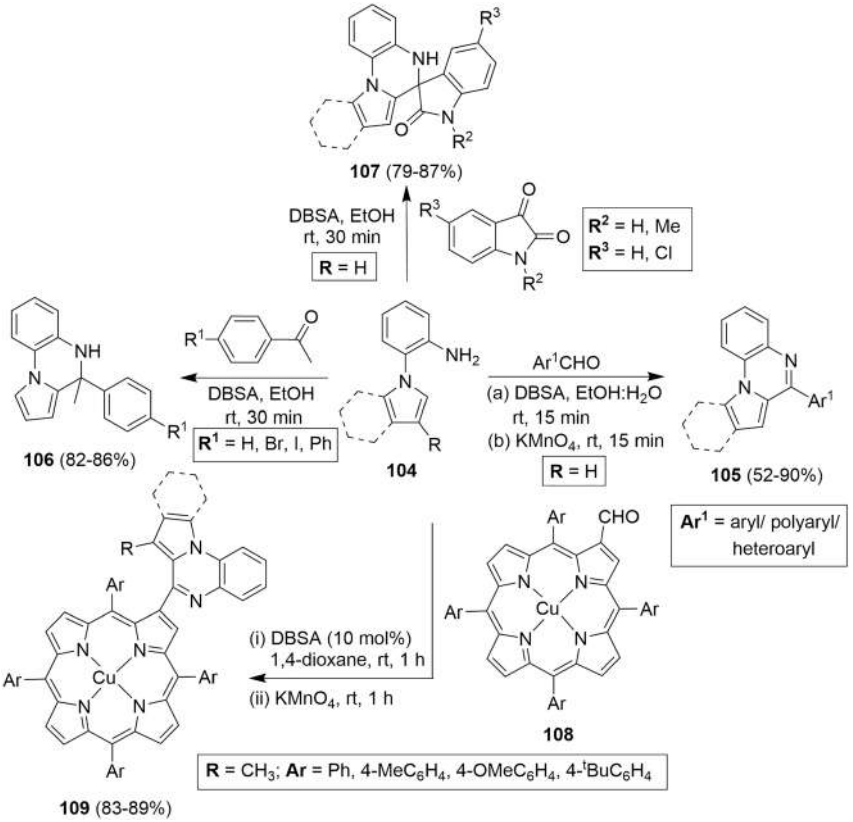


Figure 10.39: DBSA-promoted synthesis of pyrrolo- and indolo[1,2-*a*]quinoxaline derivatives.

mechanism demonstrated the role of DBSA as to activate the aldehydes by protonation of carbonyl oxygen and thereby, facilitates the nucleophilic attack of amino group to form the corresponding Schiff's base intermediate followed by an intramolecular cyclization to form pyrrolo[1,2-*a*]pyrazine-fused *meso*-tetraphenylporphyrins (**111**) [104].

It is interesting to note that, the aliphatic and electron-deficient aryl aldehydes provided the products in significantly higher yields as compared with electron-rich and heterocyclic aldehydes where the reaction was found to be sluggish and provided the products with low yields.

10.2.15 Prins cyclization reaction

The Prins cyclization is a condensation reaction of aldehydes with activated olefins under acidic conditions to synthesize 1,3-dioxane derivatives [105]. Yang and

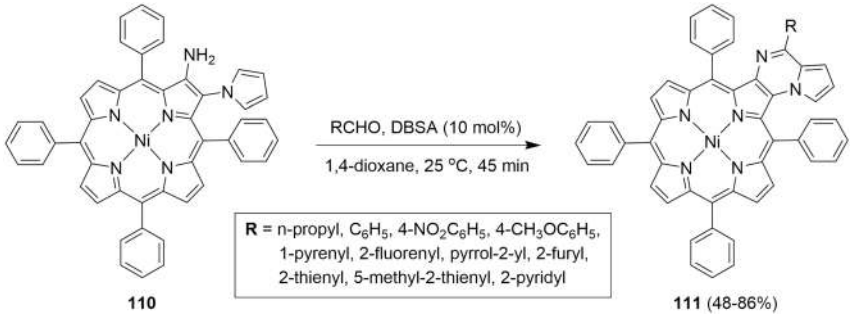


Figure 10.40: Synthesis of β,β'-fused nickel(II) pyrrolo[1,2-*a*]pyrazinoporphyrins.

co-workers carried out Prins cyclization of substituted styrenes with formaldehyde (**26**) using DBSA as a catalyst to form the 4-aryl-1,3-dioxanes (**112**) in 34–91% yields (Figure 10.41) [106]. In addition, the reaction also proceeded well with other substrates such as tertiary alcohols and acetophenone to obtain the desired 1,3-dioxane products (**113** and **114**) in good yields (Figure 10.41).

10.2.16 Strecker reaction

A multi-component green synthesis of α-aminonitriles (**115**) have been carried out by M. Shekouhy through the reaction of a series of aryl or alkylamines (**20**), aldehydes (**81**) and trimethylsilylcyanide (TMSCN) in presence of sulfuric acid-modified polyethylene glycol 6000 (PEG-OSO_3H) as the surfactant-catalyst in water at room temperature

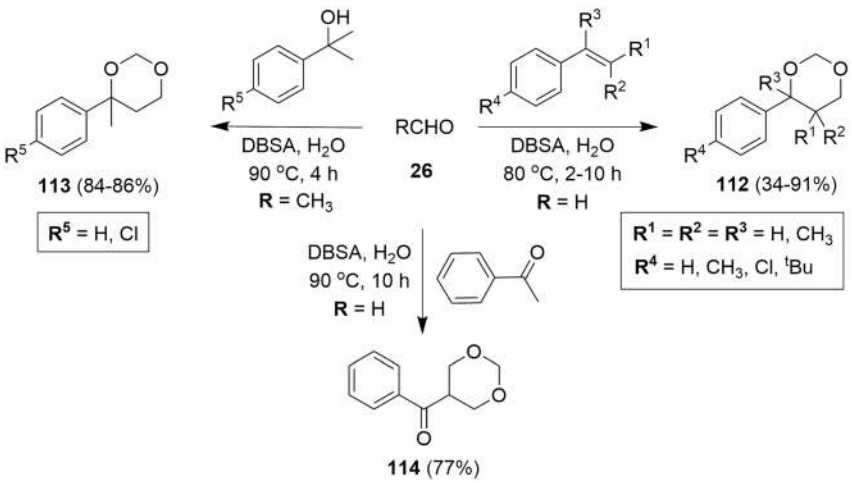


Figure 10.41: DBSA-catalyzed synthesis of diverse1,3-dioxane analogues.

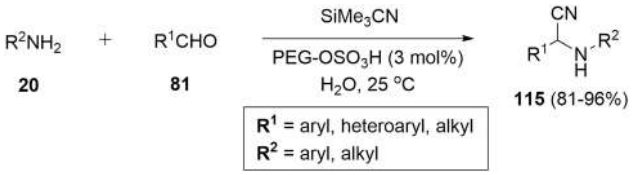


Figure 10.42: PEG-OSO_3H-catalyzed synthesis of α-aminonitriles in water.

(Figure 10.42). Interestingly, the desired products (**115**) were obtained in excellent yields [107]. Additionally, this methodology involves an inexpensive and biodegradable catalyst which provided cleaner reaction profile and simple workup procedures to isolate the desired products (**115**).

10.2.17 Thioacetalization reaction

Thioacetalization reaction involves the synthesis of thioacetal derivatives by the condensation of carbonyl compounds with low molecular weight thiols or dithiols in the presence of acidic catalysts. Thioacetal derivatives were extensively investigated as carbonyl protecting groups that are used in many multi-step organic syntheses. The main demerit associated with thioacetalization reactions is the use of thiols which are flammable, harmful and odorous reagents having various safety problems. To overcome these safety issues, a chemoselective thioacetalization of carbonyl compounds (**116**) was performed in the presence of DBSA by using 3-(1,3-dithian-2-ylidene) pentane-2,4-dione (**117**) as a thiol synthetic equivalent in aqueous medium (Figure 10.43). Addition of a catalytic amount of DBSA in the reaction mixture forms a white turbid emulsion initially and it was believed that the reaction takes place inside the micelles. Due to the hydrophobic nature of the core of micelles, water formed during the reaction is expelled out of the core, thus accelerating the rate of reaction to produce desired products (**118**) in moderate to high yields. This synthetic strategy was

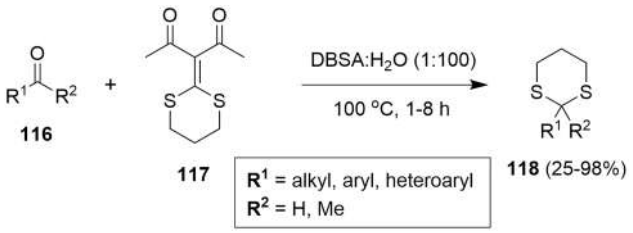


Figure 10.43: DBSA-catalyzed thioacetalization of carbonyl compounds to form 1,3-dithiane analogues.

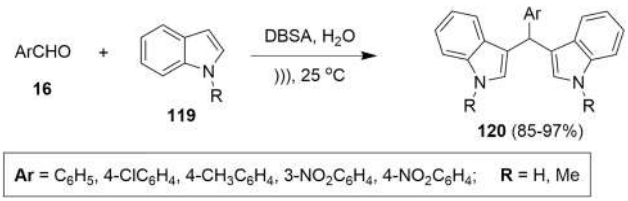


Figure 10.44: Synthesis of bis(indolyl)methanes under ultrasonic conditions.

later applied for the production of a series of diverse thioacetal analogues (**118**) by using a mixture of DBSA and water in 1:100 M ratio [108].

10.3 Miscellaneous organic transformations

10.3.1 Synthesis of bis(indolyl)methanes

The *p*-dodecylbenzenesulfonic acid-catalyzed eco-friendly synthesis of bis(indolyl) methanes (**120**) have been reported by Xu and co-workers [109] where an ultrasound-assisted reaction was carried out between aromatic aldehydes (**16**) and indole or *N*-methylindole (**119**) using DBSA as the Bronsted acidic catalyst in water at ambient temperature (Figure 10.44). This method was found to be superior over previously reported methods [110] to construct the bis(indolyl)methanes (**120)** in excellent yields using an eco-friendly approach.

10.3.2 Synthesis of hydrazones

The amidinohydrazone scaffolds have been used as starting materials to synthesize numerous natural products and drug molecules [111, 112]. Chen et al. have reported [113] a green synthesis of 2-(1,5-diaryl-1,4-pentadien-3-ylidene)-hydrazinecarboximidamide hydrochloride analogues (**123**) in good yields through a DBSA-catalyzed condensation reaction of chalcones (**121**) with aminoguanidine hydrochloride (**122**) in aqueous medium at ambient temperature under ultrasonic conditions (Figure 10.45).

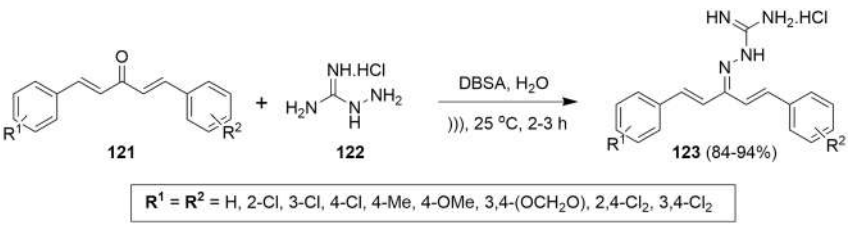


Figure 10.45: Synthesis of 2-(1,5-diphenyl-1,4-pentadien-3-ylidene)-hydrazinecarboximidamide hydrochloride.

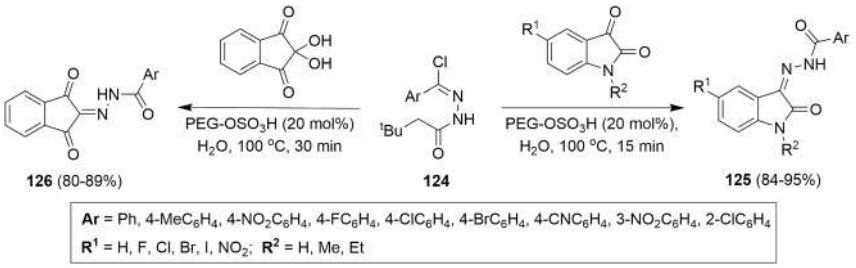


Figure 10.46: Synthesis of isatin and ninhydrin-based hydrazones.

Pramanik and co-workers have introduced the synthesis of isatin and ninhydrin-based hydrazones (**125** and **126**) through the reaction of *N*-(3,3-dimethylbutanoyl) arylhydrazonoyl chloride (**124**) with isatin and ninhydrin derivatives, respectively, in water containing catalytic amount of PEG-OSO_3H under reflux conditions (Figure 10.46). In this case, the catalyst displayed its dual behavior and act as Bronsted acidic and phase transfer catalyst which provided the products in excellent yields via simple filtration [114].

10.3.3 Synthesis of *β*-ketothioesters

α-Oxo ketene dithioacetals are multipurpose synthons in synthetic organic chemistry due to their role as versatile building blocks in many organic transformations [115]. Besides, *β*-ketothioesters were previously used as precursors for the synthesis of a wide range of natural products [116]. Hence, an environment-friendly hydrolysis of *α*-oxo ketene dithioacetals (**127**) has been developed by Feng and co-workers [117] to construct a series of *β*-ketothioesters (**128**) in excellent yields using DBSA as a Bronsted acidic catalyst in water under reflux conditions (Figure 10.47).

10.3.4 Synthesis of thioethers

Many researchers around the globe have synthesized thioethers *via* Ullmann S-arylation [118] reactions which include metal-catalyzed substitution of aryl halides

Figure 10.47: Synthesis of *β*-ketothioesters in water containing DBSA as Bronsted acidic catalyst.

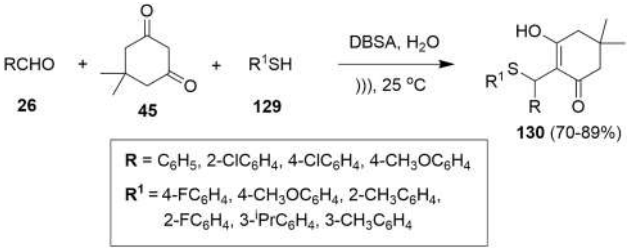


Figure 10.48: Synthesis of 3-hydroxy-5,5-dimethyl-2-[aryl(arylthio)methyl]cyclohex-2-enones.

with aryl sulfides, and a thia-Michael addition [119] of sulfur nucleophiles to α,β-unsaturated carbonyl compounds. Yang et al. reported [120] ultrasound-assisted one-pot three-component reaction of aromatic aldehydes (**26**) with dimedone (**45**) and thiophenols (**129**) in water using DBSA as a catalyst to afford 3-hydroxy-5,5-dimethyl-2-[aryl(arylthio)methyl]cyclohex-2-enone derivatives (**130**) in high yields (Figure 10.48).

10.3.5 Synthesis of urea, carbamates and S-thiocarbamates

Inaloo et al. have reported the solvent-free synthesis of carbamates (**132**), S-thiocarbamates (**133**) and urea derivatives (**134**) by incorporating DBSA as a catalyst [121]. The transformation of various substituted phenols, thiophenols and anilines (**131**) was carried out by reacting them with cyanate salts in the presence of DBSA catalyst under the solvent-free conditions to afford the primary carbamates (**132**), S-thiocarbamates (**133**) and urea derivatives (**134**), respectively, in moderate to high yields (Figure 10.49). Various acids such as HCl, H_2SO_4, PTSA, $HClO_4$, CCl_3COOH and CF_3COOH, were screened to catalyze these reactions, however, only DBSA was able to promote the reaction and produced the desired products in excellent yields.

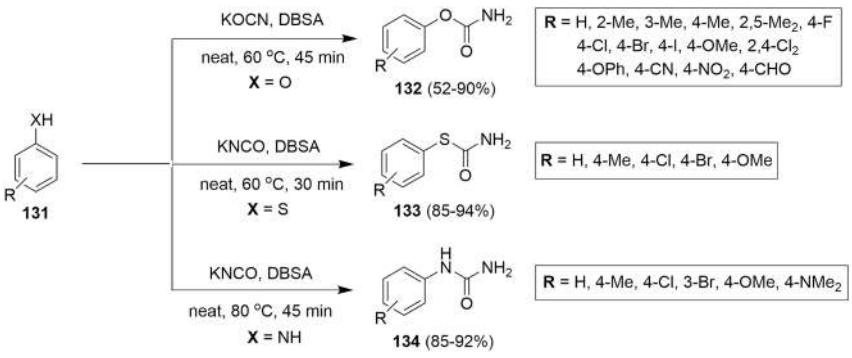


Figure 10.49: DBSA-catalyzed solvent-free synthesis of carbamates, S-thiocarbamates and urea derivatives.

10.4 Conclusions

In summary, this article presents an overview on diverse organic transformations catalyzed by Bronsted acidic surfactants to construct a variety of aromatic, heteroaromatic and fused heterocyclic molecules. The methods presented herein include a brief discussion about the comparison of catalytic efficiency and recyclability of Bronsted acidic catalysts for developing various environmentally benign reaction conditions. In addition, a number of eco-friendly procedures have also been described to synthesize various organic molecules of pharmaceutical and material interests. Furthermore, this survey encourages the synthetic chemists to design efficient one-pot green strategies for the construction of biologically and materially relevant organic compounds using eco-compatible Bronsted acidic surfactant combined catalysts under mild and solvent-free conditions.

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11 The aryl iodine-catalyzed organic transformation via hypervalent iodine species generated *in situ*

Abstract: The application of hypervalent iodine species generated *in situ* in organic transformations has emerged as a useful and powerful tool in organic synthesis, allowing for the construction of a series of bond formats via oxidative coupling. Among these transformations, the catalytic aryl iodide can be oxidized to hypervalent iodine species, which then undergoes oxidative reaction with the substrates and the aryl iodine regenerated again once the first cyclic cycle of the reaction is completed. This review aims to systematically summarize and discuss the main progress in the application of *in situ*-generated hypervalent iodine species, providing references and highlights for synthetic chemists who might be interested in this field of hypervalent iodine chemistry.

Keywords: catalytic cycle; C–X bond formation; environmental benign reagents; hypervalent iodine chemistry; *in situ*-generated hypervalent iodine species; rearrangement.

11.1 Introduction

In the past several decades, hypervalent iodine(III) reagents have been well developed and widely used in various organic transformations due to their unique reactivity that can be considered as versatile and environmental benign alternative to the toxic heavy metals [1–6]. Although hypervalent iodine reagents have so many advantages, there still exist some problems such as solubility and waste production, which in a sense limit their further development and wide application [7–9]. Therefore, research on hypervalent iodine species generated *in situ* with the purpose of avoiding use of stoichiometric amount of oxidant and achieving atom economy has attracted increasing attention in the fields of green chemistry.

With continuous development, the synthetic chemists have found that the *in situ*-generated hypervalent iodine reagents not only retains all the advantages of hypervalent iodine reagents, but also avoids the problems of preparation and purification [10].

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Whereafter, large amounts of *in situ*-generated hypervalent iodine compounds have been extensively investigated, [11, 12, 30–135] and several reviews on the synthesis and properties of *in situ*-generated hypervalent iodine species have been published [13–26]. In general, the application of hypervalent iodine species, which could be generated *in situ* by oxidation of iodoarenes in the presence of a suitable terminal oxidant such as *m*-chloroperbenzoic acid (*m*CPBA), AcO_2H or oxones, are gaining rapid progress in the field of hypervalent iodine chemistry [27–29].

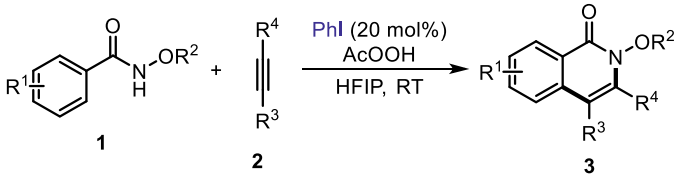
Here, this review summarizes the recent advances of the *in situ* formed hypervalent iodine species-mediated organic transformation, which comprise new synthetic applications, mechanisms and concepts. Based on the reaction types, the scope of these transformations encompasses formation of C–C bond, formation of C–O bond, formation of C–N bond, formation of C–X bond, and rearrangement reactions.

11.2 Formation of C–C bonds

C–C bond formation reaction, a class of important transformation, has hence received increasing research interest in the field of agrochemicals and pharmaceuticals during the several decades. The construction the C–C bond mediated by hypervalent iodine species generated *in situ*, which meets well the standards of the green chemistry, has been found a powerful approach to access the densely functionalized skeletons that hold great potential in the synthesis of structurally complicated molecules. The existing strategies of C–C bond formation mediated by hypervalent iodine species generated *in situ* could be divided into the following several types.

11.2.1 Construction of C(sp^2)–C(sp) bonds

In 2014, Antonchick's group [30] reported a straightforward metal-free protocol employing hypervalent iodine species produced *in situ* as oxidant for the synthesis of isoquninolone derivatives **3** from the reaction of benzamide derivatives **1** and alkynes **2**. This C(sp^2)–C(sp) bond formation strategy has the advantages of readily available reagents, fast reaction rate, broad substrate scope and high functional group tolerance. A possible mechanism was proposed as follows: first, the reaction of iodobenzene with peracetic acid resulted in the formation of PIDA *in situ*, which would oxidize *N*-alkoxybenzamides **1** to give nitrenium ion intermediates **5**, together with the regeneration of iodobenzene which entered the next catalytic cycle. Subsequently, nitrenium ions **5** could be attacked by alkyne **2** to form carbenium ion intermediates **6**, which were converted to title products **3** through an intramolecular Friedel–Crafts process (Figure 11.1).



Plausible mechanistic pathway:

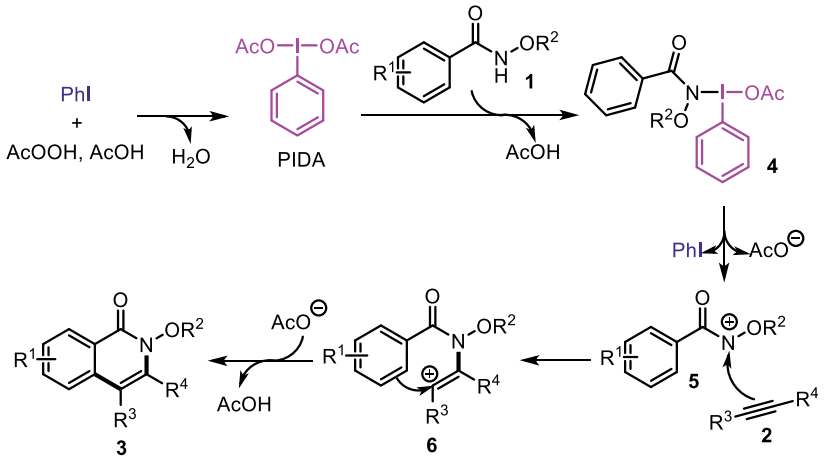
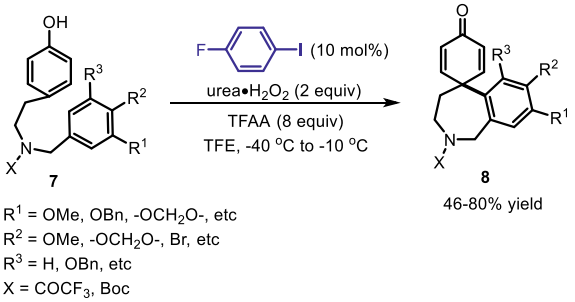


Figure 11.1: Synthesis of isoquinolone derivatives via C(sp^2)–C(sp) bond formation mediated by I(III) generated *in situ*.

11.2.2 Construction of C(sp^2)–C(sp^2) bonds

In 2008, Kita's group [31] discovered an effective iodoarene-catalyzed method for the synthesis of a series of spirocyclic dienones **8** from the phenols **7** via C(sp^2)–C(sp^2) bond formation. It was postulated that hypervalent iodine(III) species was generated *in situ* from the oxidation of iodoarene by alternative oxidant bis(trifluoroacetyl) peroxide, which was derived from TFAA and H_2O_2. Then the reactive iodine(III) species reacted with substrate phenols **7** to give phenoxy iodine(III) intermediates **9**, which could be converted to the reactive cationic intermediates **10** through liberation of iodoarene. Finally, the cation of intermediate **10** was attacked by internal π-nucleophile at the *ipso*-carbon to produce the corresponding spirocyclized product **8** (Figure 11.2).



Plausible mechanistic pathway:

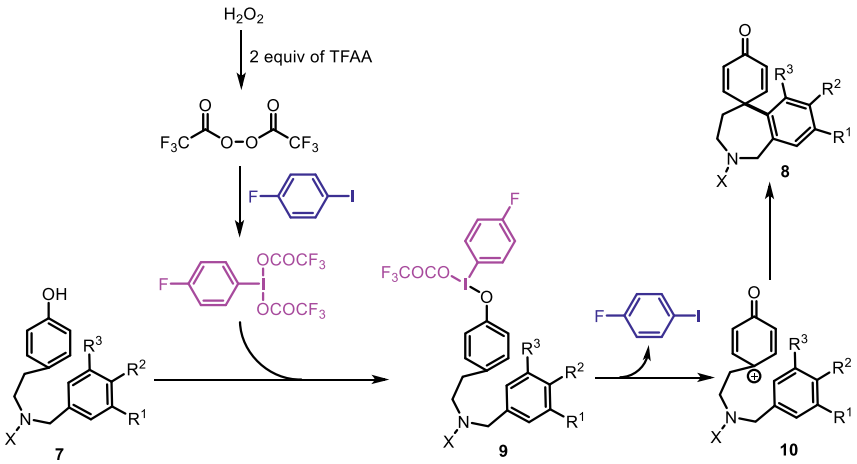
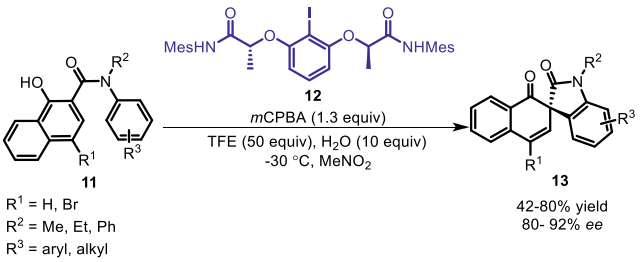


Figure 11.2: Synthesis of spirocyclic dienones via C(sp^2)–C(sp^2) bond formation mediated by I(III) generated *in situ*.

The chiral hypervalent moiety generated *in situ* from the oxidation of chiral aryl iodide is a useful reagent in enantioselective C(sp^2)–C(sp^2) bond formation reactions. In 2015, Gong and coworkers [32] described that chiral hypervalent iodine species **14**, which was derived *in situ* from the oxidation of chiral aryl iodine **12** with *m*CPBA, could efficiently oxidize various 1-hydroxy-*N*-aryl-2-naphthamide derivatives **11** to the corresponding spirooxindoles and their analogs **13** through enantioselective dearomatizative spirocyclization. In this transformation, the hypervalent phenyl-λ-iodanes **14** generated *in situ* underwent a ligand exchange with the hydroxy group of substrates **11**, followed by further ligand exchange with TFE/H_2O to give intermediates **15**. Finally, an intramolecular S_N2'-like Friedel–Crafts substitution of intermediate **15** occurred, leading to the formation of the desired products **13**, together with the regeneration of chiral aryl iodine **12**. It is noteworthy that the addition of TFE and water could enhance the chemical yield and enantioselectivity of the reaction (Figure 11.3).



Plausible mechanistic pathway:

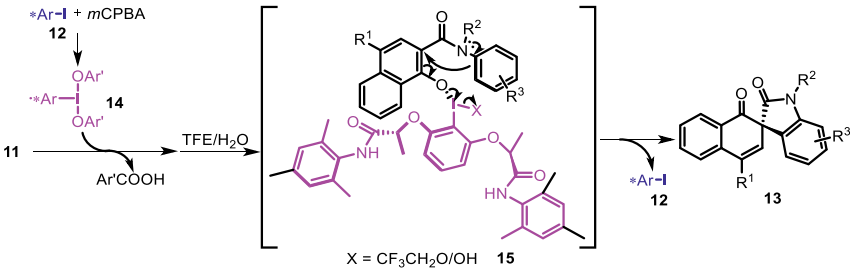
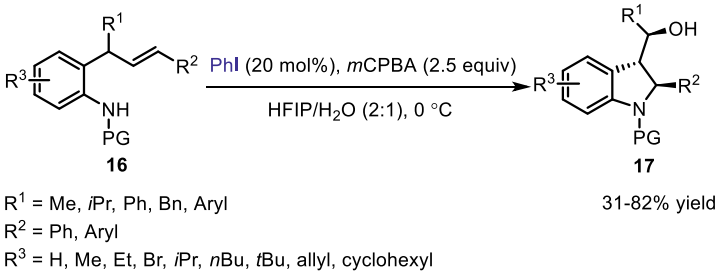


Figure 11.3: Synthesis of spirooxindole derivatives via C(sp^2)–C(sp^2) bond formation mediated by I(III) generated *in situ*.

Fan's group [33] in 2017 reported an efficient synthesis of indolin-3-ylmethanols **17** with high diastereoselectivities from 2-allylanilines **16** through hypervalent iodine(III)-mediated oxidative dearomatization and rearrangement. It was postulated that hypervalent iodine(III) species was first generated *in situ* from the reaction of PhI and *m*CPBA. Next, 2-allylanilines **16** reacted with this reactive hypervalent iodine(III) species to provide N–I intermediates **18**, which was converted to spirocyclic intermediates **19** via dearomatization induced by the *ortho*-position group after releasing a molecule of PhI. Finally, the more favorable conformer **19b** was attacked by water to yield the target compound **17** through an aromatization-triggered rearrangement (Figure 11.4).

In 2018, Yorimitsu and coworkers [34] established a metal-free dehydrogenation coupling strategy for the synthesis of 2-hydroxy-2′-iodo biaryls **21** from phenols **20** promoted by the hypervalent iodine species generated *in situ*. Notably, the protocol of using *m*CPBA to oxidize iodobenzene into hypervalent iodine species *in situ* could effectively solve the preparation difficulties of aryliodanes, due to its instability and difficult purification. For the reaction mechanism, the hypervalent-iodine-tethered intermediates **22** was formed through ligand exchange on the hypervalent iodine atom, followed by a [3,3] sigmatraopic rearrangement to afford the target product biaryls **21** (Figure 11.5).



Plausible mechanistic pathway:

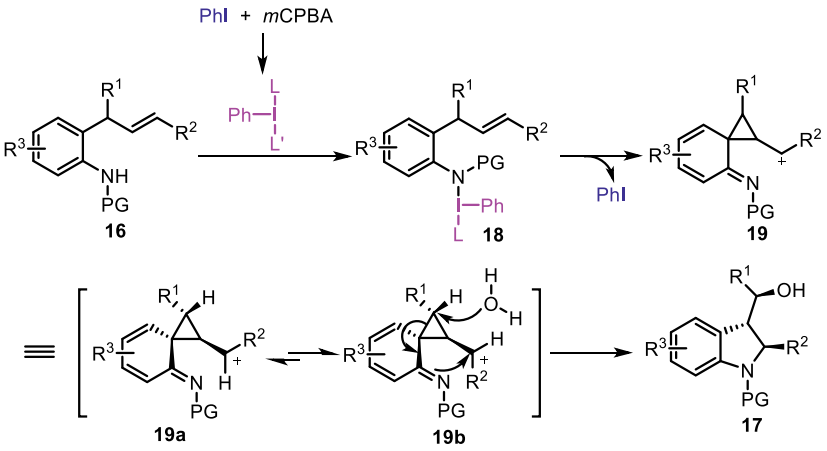


Figure 11.4: Synthesis of functionalized indolin-3-ylmethanols via C(sp^2)–C(sp^2) bond and C–N bond formation mediated by I(III) generated *in situ*.

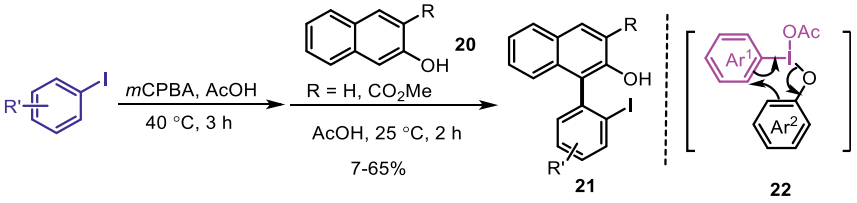
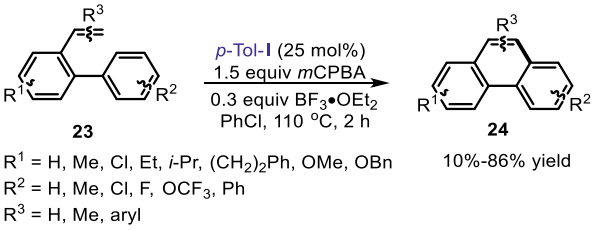


Figure 11.5: Synthesis of 2-hydroxy-2′-iodobiaryls via C(sp^2)–C(sp^2) bond formation mediated by I(III) generated *in situ*.

In 2018, Murphy and colleagues [35] reported a metal-free oxidative C–H coupling reaction between arene and alkene with *in situ*-generated hypervalent iodine species, leading to the formation of polycyclic aromatic hydrocarbons **24**. Mechanistically, iodotoluene first reacted with *m*CPBA to form the hypervalent iodine(III) species *in situ*,

which was activated by $BF_3{\cdot}OEt_2$, and then attacked by olefins **23** to give the benzylic cations **25**. Subsequently, the deprotonation of intermediates **25** delivered vinyliodonium intermediates **26**, which were converted to vinylenephenonium ions **27**. Finally, the target products **24** were obtained from intermediates **27** through ternary ring opening and aromatization (Figure 11.6).



Plausible mechanistic pathway:

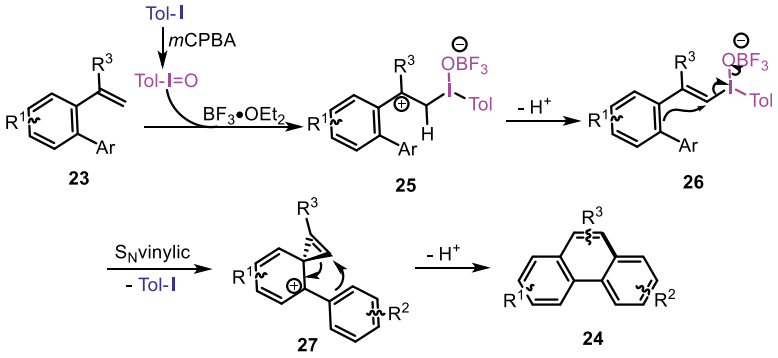


Figure 11.6: Synthesis of polycyclic aromatic hydrocarbons via C(sp^2)–C(sp^2) bond formation mediated by I(III) generated *in situ*.

11.2.3 Construction of C(sp^2)–C(sp^3) bonds

In recent years, the asymmetric oxidative coupling of two individual C–H bonds has attracted a great deal of attention from organic chemists. In 2014, Gong and collaborators [36] disclosed a highly enantioselective method for synthesizing spirooxindoles **30** via an asymmetric oxidative intramolecular C(sp^2)–C(sp^3) coupling cyclization of N^1,N^3-diphenylmalonamides **28** mediated by the chiral hypervalent iodine, which were generated *in situ* with chiral iodine reagent **29** being oxidized by peracetic acid. For the absolute configuration of the products **30**, the *Si* face of the iodo-enol intermediates **31**

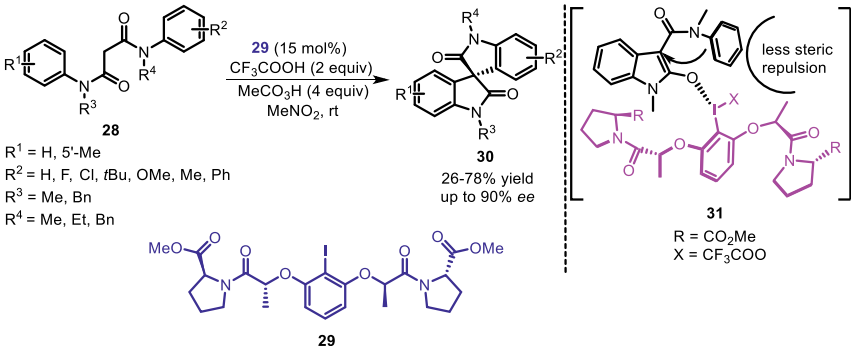
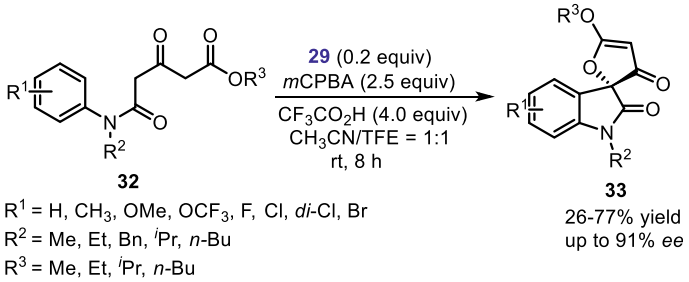


Figure 11.7: Synthesis of spirooxindoles via C(sp^2)–C(sp^3) bond formation mediated by I(III) generated *in situ*.

formed by intramolecular Friedel-Crafts addition was more vulnerable to the nucleophilic attack of the benzene ring (*syn* addition-elimination), as the aniline part of intermediates **31** was far away from the bulky substituents. It is noteworthy that by using chiral organoiodine compounds as catalysts, four C–H bonds were stereoselectively functionalized, which means that the chiral hypervalent organoiodine species generated *in situ* could enable enantioselective functionalization of inactive C–H bonds (Figure 11.7).

By applying the same chiral aryl iodide **29**, Du and coworkers [37] in 2016 realized the asymmetric synthesis of a series of substituted spirofurooxindoles **33** via an enantioselective organocatalytic oxidative spirocyclization of alkyl 3-oxopentanedioate monoamide derivatives **32**. The reaction process involved first the generation of the chiral hypervalent(III) iodine species *in situ* from chiral aryl iodide **29** and *m*CPBA, and then the formation of the C–I(Ar) bond intermediates **34** from reaction between the chiral hypervalent iodine(III) and substrates **32**. Subsequently, intermediates **34** underwent C(sp^3)–O bond formation to form intermediates **35**. Next, another C(sp^3)–I bond formation occurred to transform intermediates **35** to chiral intermediates **36**. Finally, the *Si* face of configuration **36** was nucleophilically attacked by the benzene ring, realizing C(sp^2)–C(sp^3) bond formation and C(sp^3)–I bond cleavage to form the corresponding spirofurooxindole products **33** (Figure 11.8).

In 2015, Shafir and coworkers [38, 39] found that the *in situ*-generated hypervalent iodine $ArI(O_2CCF_3)_2$ from the reaction of iodoarenes **38** and Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) or *m*CPBA could be effectively used as oxidants to synthesize α-arylated carbonyl compounds **39** from 2-cyanoketones **37** via direct oxidative C(sp^2)–C(sp^3) bond coupling. It is worth noting that Oxone could not only be used as an oxidant for hypervalent activation of ArI (via $KHSO_5$), but also accelerate the formation of intermediates **40** (via K_2SO_4). In contrast, the solely use of *m*CPBA gave a low rate because it could only be used as an oxidant (Figure 11.9).



Plausible mechanistic pathway:

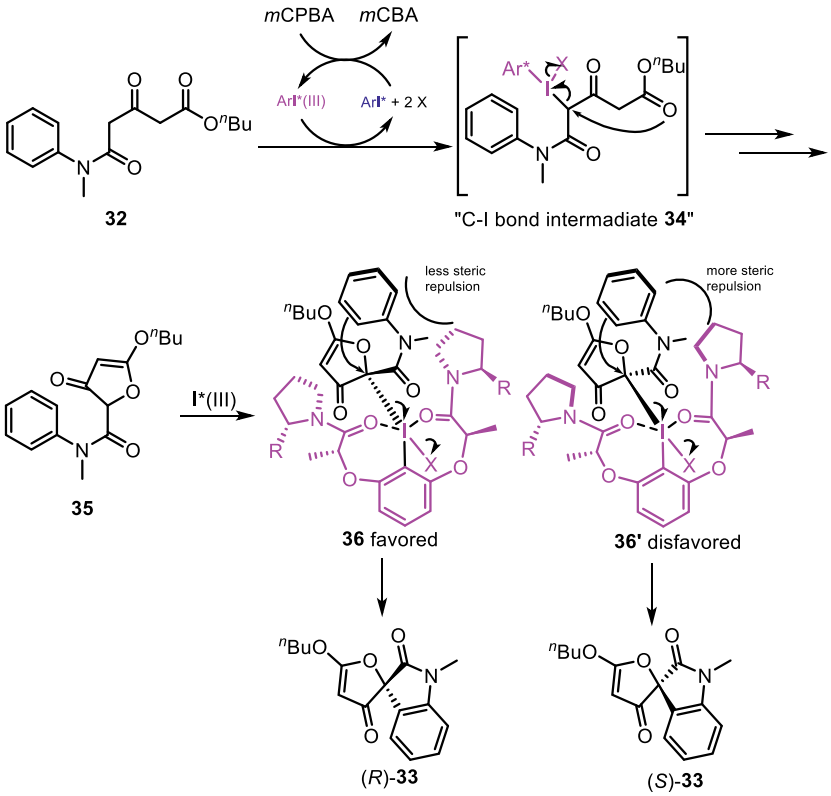


Figure 11.8: Synthesis of substituted spirofurooxindoles via C(sp^2)–C(sp^3) bond and C(sp^3)–O bond formation mediated by I(III) generated *in situ*.

In 2019, Du et al. [40] reported that $PhI(OMe)_2$, which was generated *in situ* from the reaction of PhIO with MeOH, could catalyze the intramolecular C(sp^2)–C(sp^3) oxidative coupling of *N*-arylamide derivatives **41** to deliver the corresponding spirooxindole

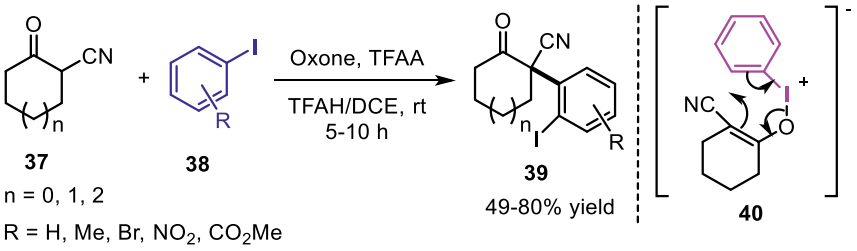
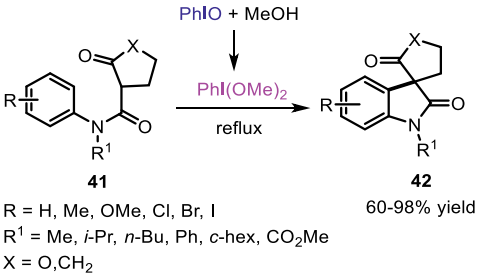


Figure 11.9: Synthesis of α-arylated carbonyl compounds via C(sp^2)–C(sp^3) bond formation mediated by I(III) generated *in situ*.

compounds **42** in high yields. It was proposed that the enol form of substrates **43** reacted with $PhI(OMe)_2$ to generate the O–I bond intermediates **44**, which underwent 1,3-migration to give the I–C bond intermediates **45.** Next, the intramolecular cyclization occurred in intermediates **45** to construct the C–C bond by loss of one molecular of phenyliodine and methoxide to afford the iminium salt **46.** Finally, aromatization was realized via the abstraction of a proton from **46**, giving the desired product **42** (Figure 11.10).



Plausible mechanistic pathway:

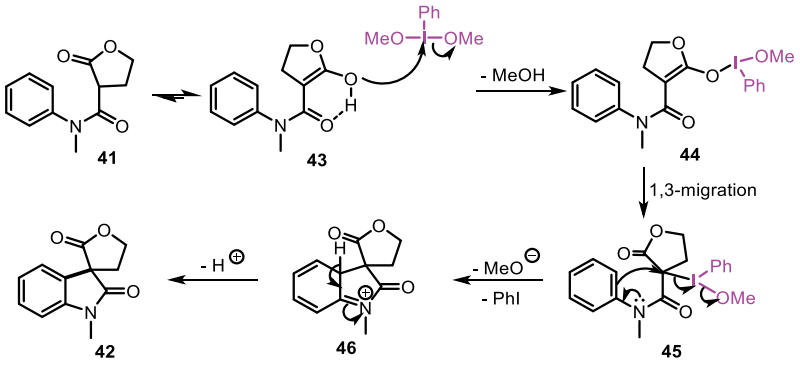


Figure 11.10: Synthesis of spirooxindole compounds via C(sp^2)–C(sp^3) bond formation mediated by I(III) generated *in situ*.

11.3 Formation of C–O bonds

With the vast application of hypervalent iodine species, generated *in situ* from the oxidation of aryl iodide, a vast number of organic transformations involving C–O bond formation have also been realized under more environmentally benign conditions. Categorization of these C–O bond formations are as follows:

11.3.1 Lactonization

It is noteworthy that heterocycles are commonly found in natural products, bioactive compounds and chiral ligands, and many synthetic methods have been developed for the construction of heterocyclic skeleton. Among them, many were realized utilizing hypervalent iodine species generated *in situ*.

In 2005, Kita and coworkers [41] demonstrated a convenient method for the synthesis of spiroheterocyclic products **48** from phenolic propionic acid derivatives **47** catalyzed by aryl iodine. The hypervalent iodine species was formed *in situ* with 4-iodotoluene being oxidized by *m*CPBA. It was worth noting that this strategy could avoid the waste of hypervalent iodine reagent with stoichiometric ratio by using recyclable arene iodide as catalyst and *m*CPBA as terminal oxidant (Figure 11.11).

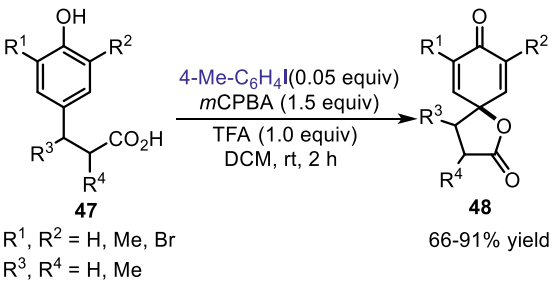


Figure 11.11: Synthesis of spiroheterocyclic products via spirolactonization mediated by I(III) generated *in situ*.

In 2008, Kita's group [42] first found that naphthol substrates **49**, after being treated with the *in situ*-generated chiral iodine(III) derived from chiral iodoarene **51** and *m*CPBA, could undergo enantioselective oxidative dearomatizing spirolactonization to produce the corresponding chiral *oxo*-spirocycles **50a** and **50b**. This shows that chiral iodine compounds could provide a new entrance to asymmetric organocatalysis, although the enantioselectivity needs to be improved. A few years later, the same group [43] designed and prepared a series of new spirobiindane-based chiral iodoarenes, having some substituents at the *ortho*-aryl ring position relative to the iodine atom. It was found these chiral iodoarenes could significantly improve the enantioselectivity of the target product **50c** from substrate naphthols **49**. Through the comparison of

various *ortho*-functionalized iodoarene catalysts, it was determined that *o*-ethyl-substituted iodoarene **52** was best iodoarene catalyst in terms of both reactivity and enantioselectivity. Recently, Kita and coworkers [44] reported a new type of atropisomeric biaryl molecules bearing the iodine atoms in the major groove of the naphthalene rings, and had them applied to the synthesis of the chiral oxo-spirocycles **50d** via asymmetric dearomatizing spirolactonization of naphthol carboxylic acids **49**. Especially, 2,2′-dimethyl iodoarene derivative **53** displayed a promising level of asymmetric control up to 78% *ee* (Figure 11.12).

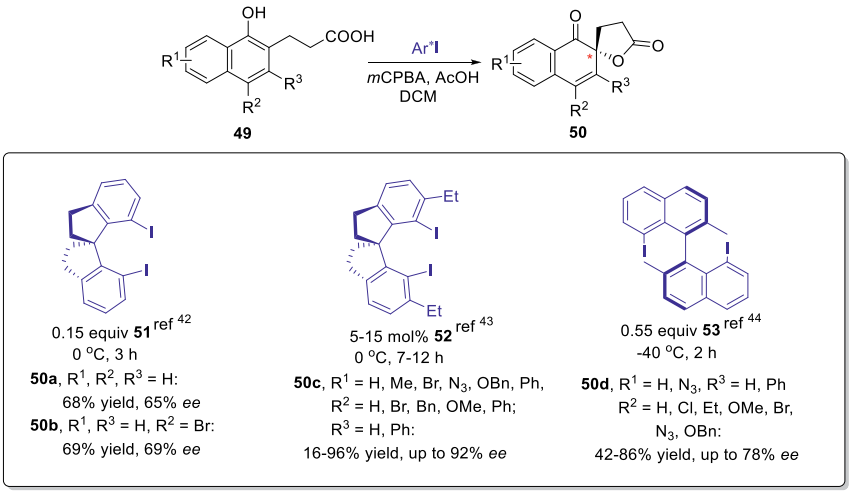


Figure 11.12: Synthesis of chiral oxo-spirocycles via spirolactonization mediated by I(III) generated *in situ*.

Subsequently, the variants of chiral hypervalent iodine precursors that promote this transformation were further investigated. In 2010, Ishihara and coworkers [45] developed an enantioselective Kita oxidative spirolactonization of the substituted phenolic propionic acids **54** using chiral iodoarene **56** as catalyst and *m*CPBA as terminal oxidant, leading the formation of spirolactonic *ortho*-quinol esters **55a** with *ee* value up to 92%. Mechanistically, the C_2-symmetric iodoarene **56** was oxidized by *m*CPBA to form conformationally flexible hypervalent organoiodines(III) *in situ*, and the intramolecular secondary $n–\sigma^*$ or hydrogen-bonding interactions between the acidic amido protons and the iodine(III) ligands produced a chiral environment. In 2017, the same research group [46] also reported the reaction of 2-naphthol derivatives **54** with conformationally flexible 2-aminopropanol-based iodoarene **57** in the presence of *m*CPBA and HFIP, which produced spirolactones **55b** with high yields and excellent *ee* value through enantioselective oxidative dearomatization (Figure 11.13).

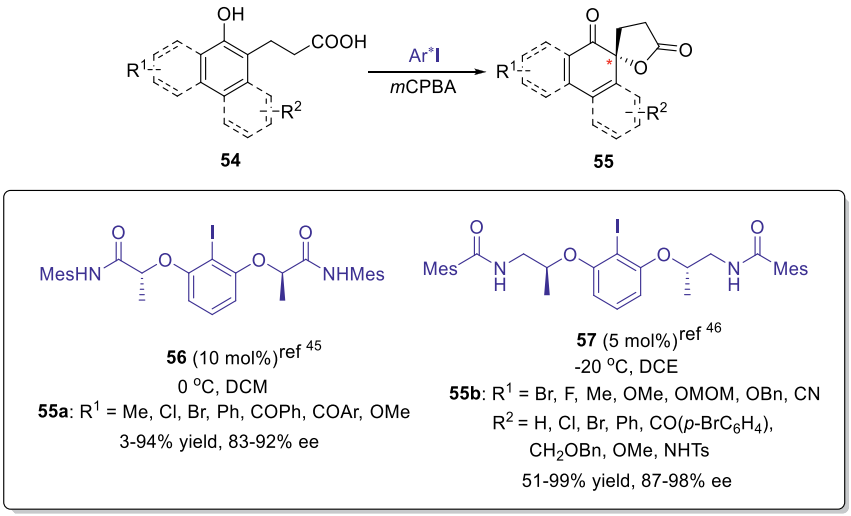


Figure 11.13: Synthesis of spirolactones via spirolactonization mediated by I(III) generated *in situ*.

In 2015, Ibrahim and coworkers [47] developed a new iodoarenes **60**, which has C_2-symmetry with an all carbon *anti*-dimethanoanthracene skeleton. Iodoarenes **60** could react with *m*CPBA and propanoic acid tethered 1-napthol derivatives **58** to produce spirolactone **59a** with an *ee* values of between 18 and 67%. Later on, Masson and coworkers designed and synthesized a new class of axially chiral iodoarenes **61** [48], which could be used as catalysts for the Kita's enantioselective oxidative spirolactonization of phenol derivatives **58**. By treating phenols **58** with the *in situ*-generated hypervalent iodine in DCM at 0 °C, the oxo-spirocyclizative compounds **59b** were obtained with moderate *ee* values. It is worth noting that the 3,3′-diaryl substituents and the H-bond amide donor in the octahydrogenated BINI backbone were key structural features for the control of stereoselectivity of iodoarenes **61**. In 2017, Nachtsheim et al. [49] also described a new C_1-symmetric triazole-functionalized chiral iodoarene **62**, which could mediate this asymmetric dearomatization spirocyclization of phenol derivatives through the *in situ*-generated hypervalent iodine species. The target product **59c** was obtained in good yields and with high *ee* values (Figure 11.14).

In addition to C_2-symmetric iodoarenes, C_1-symmetric iodoarene can also catalyze the asymmetric spirolactonization and add to a growing family of chiral organoiodine reagents. In 2019, Zheng and coworkers [50] applied this C_1-symmetric iodoarene based on [2.2]para cyclophane skeleton **65** to the enantioselective intramolecular dearomative lactonization of naphtholic propionic acids **63**, resulting in the synthesis of the corresponding spirolactones with a tetrasubstituted stereocenter **64a** in good enantioselectivities (up to 72% *ee*) under mild reaction conditions (Figure 11.15).

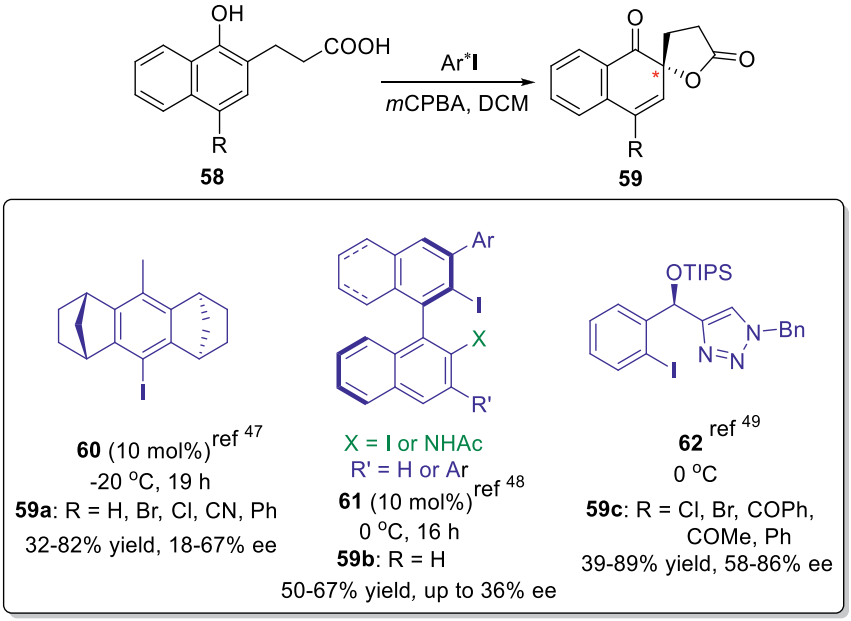


Figure 11.14: Synthesis of chiral oxo-spirocycles mediated by different chiral I(III) generated *in situ*.

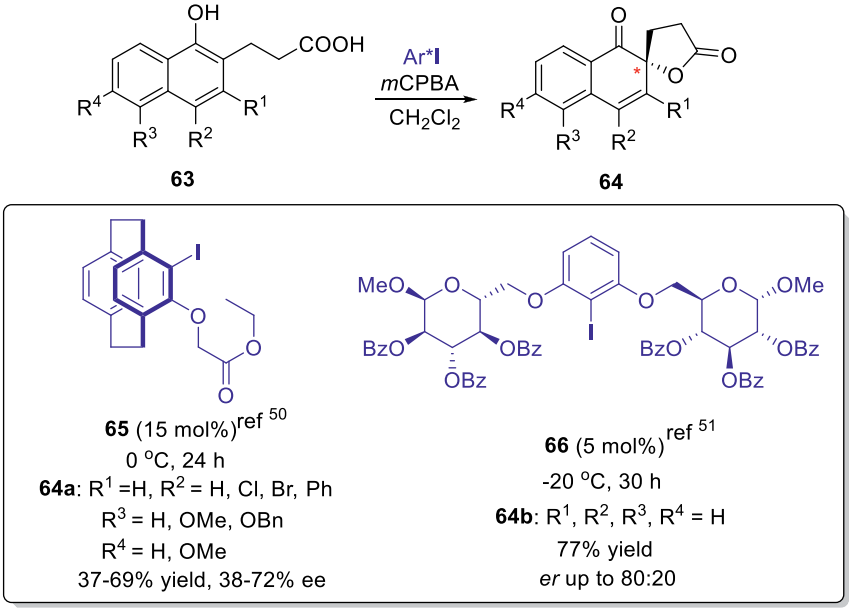


Figure 11.15: Synthesis of spirolactone derivatives via oxidative spirolactonization mediated by chiral I(III) generated *in situ*.

In 2019, Ziegler's group [51] realized the enantioselective dearomative spirocyclization of 3-(1-hydroxynaphthalen-2-yl) propanoic acid **63** to afford the corresponding spirolactones **64b** catalyzed by diverse carbohydrate-based chiral iodoarenes, which were synthesized from known compounds in one-step via Mitsunobu reaction and could be oxidized by *m*CPBA to give the corresponding hypervalent iodine(III) species. According to the results, the chiral catalyst **66** turned out to give the best *er* value of 80:20 with 77% yield (Figure 11.15).

Recently, Quideau, Peixoto's group [52], and Moran's group [53] also synthesized some novel chiral iodoarenes, which could effectively catalyze the dearomatizing cyclization of naphthyl amide.

In 2009, Ishihara and coworkers [54] illustrated a transition metal-free oxylactonization reaction to transform the ketocarboxylic acids **67** into ketolactones **68**, via *in situ* generated Koser's reagent by oxidation of PhI and *m*CPBA under acidic condition (Figure 11.16).

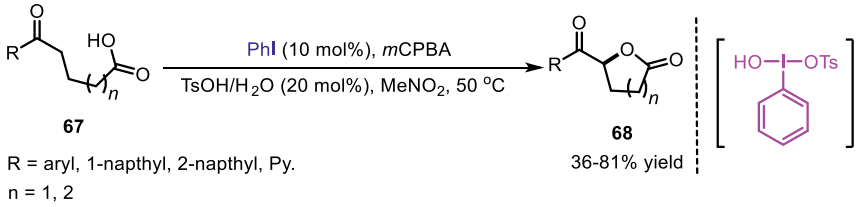


Figure 11.16: Synthesis of spirolactone via oxylactonization mediated by I(III) generated *in situ*.

In 2014, Martin's group [55] demonstrated an alternative approach for the synthesis of benzolactones **70** and 5*H*-pyrrolo[1,2-α][3,1]benzoxazinones **72** through a tandem C(sp^2)–H and C(sp^3)–H functionalization/C–O bond formation mediated by the *in situ*-formed hypervalent iodine(III) reagent under mild conditions. The yield of the obtained products varied from 40 to 99% when different arenes were applied (Figure 11.17).

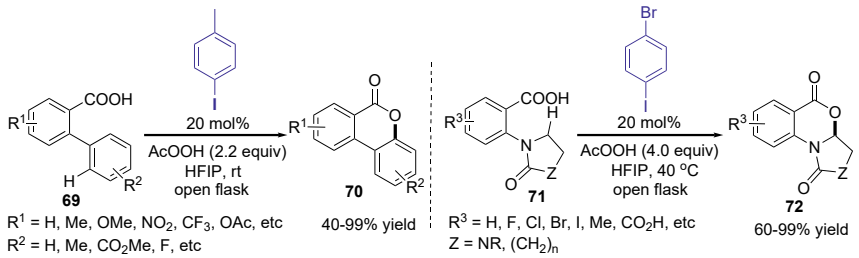


Figure 11.17: Synthesis of benzolactones and 5*H*-pyrrolo[1,2-α][3,1]benzoxazinones mediated by I(III) generated *in situ*.

In 2019, Wirth and coworkers [56] realized an enantioselective electrochemical lactonization of diketo acid derivatives **73** using chiral iodoarene **74** as redox mediators. In this electrochemical system, chiral iodoarene **74** could be converted into corresponding hypervalent iodine(III) species *in situ* by anodic oxidation without the use of stoichiometric oxidants (Figure 11.18).

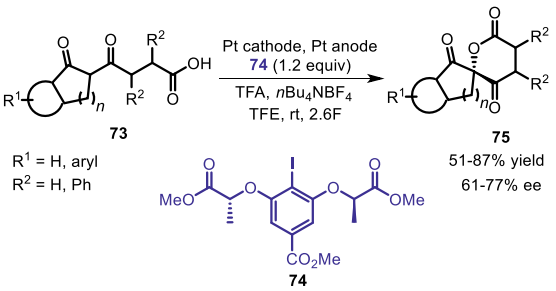


Figure 11.18: Synthesis of lactones via enantioselective electrosynthesis mediated by I(III) generated *in situ*.

11.3.2 Dearomatization

In 2011, Hutt, Lupton and coworkers [57] presented an intramolecular dearomatizing cyclization of vinylogous esters with *para*-methoxy benzyl groups **76** mediated by catalytic hypervalent iodine compound, which was produced *in situ* by treatment of PhI with *m*CPBA in HFIP/TFA. This novel mode of cyclization could rapidly access complex spirofurans **77** in good to excellent yields (Figure 11.19).

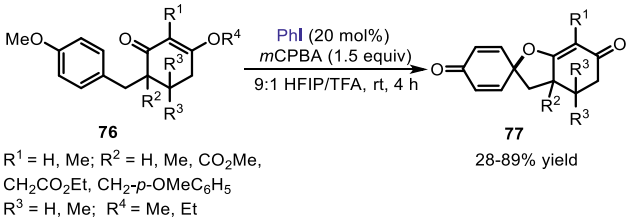


Figure 11.19: Synthesis of spirofurans by dearomatizing cyclization of vinylogous esters mediated by I(III) generated *in situ*.

In 2013, Lupton, Hutt and coworkers [58] described an organic transformation in which the commercially available *p*-MeO and *m*-MeO-substituted 3-alkoxycyclohexen-2-ones **78** were converted to oxabicyclo[3,2,1]octanes **80** and [4,2,1]nonanes **81**, respectively. This process encompasses the *in situ* conversion of ArI to hypervalent iodine species, followed with the subsequent formation of C–C and C–O bonds. Two independent nucleophiles, namely, electron-efficient aromatic rings and vinylogous esters, are very important for this cascade 1,2-olefin functionalization reaction, providing access to complex polycyclic furans (Figure 11.20).

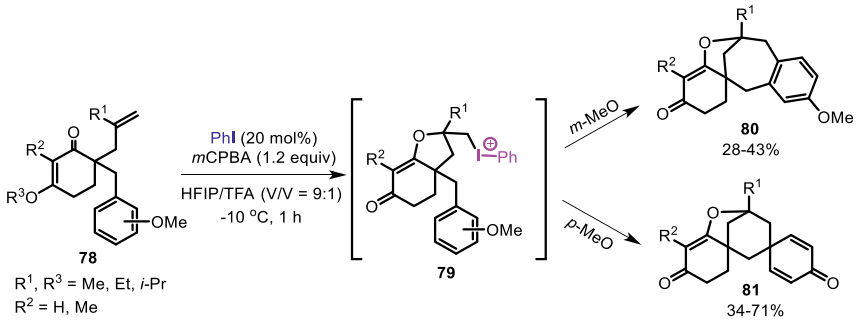


Figure 11.20: Synthesis of endo-compounds via 1,2-olefin functionalization cascade reaction mediated by I(III) generated *in situ*.

Quinones are an important class of compounds that have attracted great attention from both pharmacologists and material chemists for their interesting biologically activities and synthetic usefulness.

In 2013, Harned and colleagues [59] discovered that phenol derivatives **82** could undergo stereoselective oxidative dearomatization by reacting with the *in situ*-generated chiral hypervalent iodine compound, leading to the formation of a series of enantioenriched *para*-quinols **84**. A chiral aryl iodide catalyst **83**, which could react with *m*CPBA to form the hypervalent iodine *in situ*, was designed by DFT calculations from 8-iodotetralone and tartaric acid. Moreover, this method was suitable for synthesis of spirocycles from phenol **84** via spirocyclization (Figure 11.21).

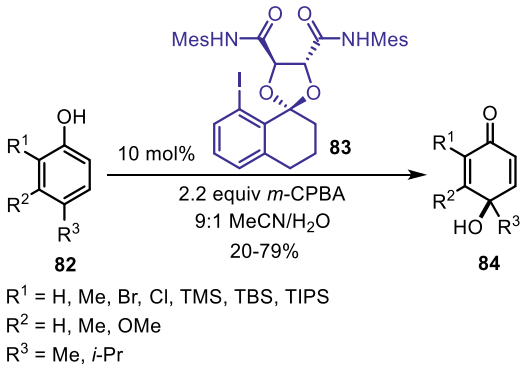


Figure 11.21: Synthesis of *para*-quinols via stereoselective oxidative dearomatization mediated by chiral I(III) generated *in situ*.

In 2019, Dohi's group [60] reported transformation of monomethoxyarenes **85** to *p*-quinones **87** via oxone/2-iodobenzoic acid-mediated regiodivergent oxidation under mild conditions. It was found that the cyclic hypervalent iodine(III) species **88** was generated *in situ* from the oxidative reaction of iodoarene **86** by oxone in water (Figure 11.22).

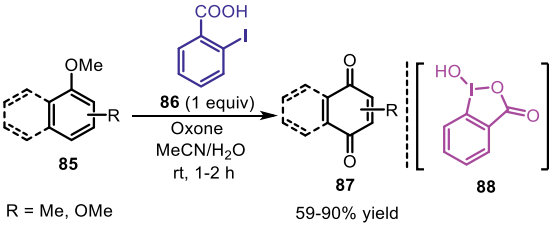


Figure 11.22: Synthesis of *p*-quinones via regiodivergent oxidation mediated by chiral I(III) generated *in situ*.

In 2016, Ishihara's group [61] reported a convenient approach to synthesize the spiroheterocycles with chiral acetal moieties **92** and **93** by chiral iodine(III)-catalyzed spiroetherification of naphthol derivatives **89** and *ortho*- and *para*-substituted phenol **90** respectively, wherein the active catalytic iodine(III) species was generated *in situ* from iodoarene **91** and *m*CPBA (Figure 11.23).

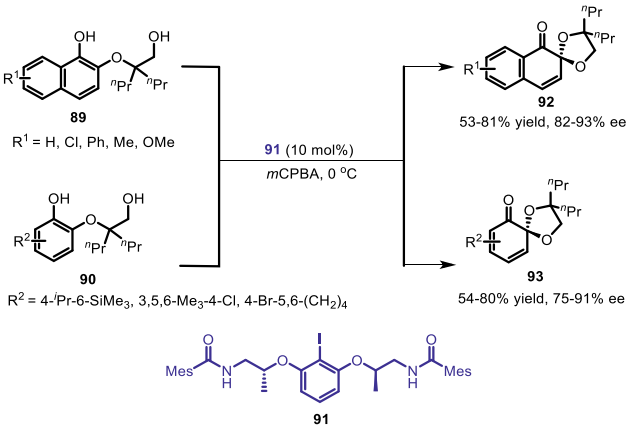


Figure 11.23: Synthesis of chiral masked *ortho*-quinones spiroheterocycles via C–O bond formation mediated by chiral I(III) generated *in situ*.

11.3.3 Alkoxylation

In 2018, Panda and Mattan [62] disclosed a one-pot two-step protocol for synthesizing 3-iodo-4-aryloxy coumarins **97** from 4-hydroxy coumarins **96**. The reaction occurred through the hypervalent iodine reagent-promoted sequential iodination and *O*-arylation of 4-hydroxy coumarins **96**. The process first forms the spiro-heterocyclic intermediate **98**, which provided the corresponding product **97** through the intramolecular migration of phenyl group from iodine to oxygen. It is worth noting that $PhI(OPiv)_2$ **95**, which is generated *in situ* from the ArI **94**, *m*CPBA, and pivalic acid, was the active hypervalent iodine species in this conversion (Figure 11.24).

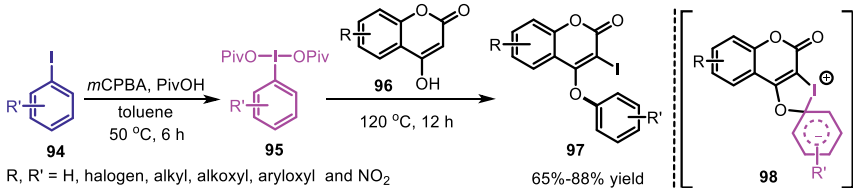


Figure 11.24: Synthesis of 3-iodo-4-aryloxy coumarins via iodination and *O*-arylation mediated by I(III) generated *in situ*.

In 2013, Fujita's group [63] reported a simple synthesis of the optically active 4-hydroxyisochroman-1-ones **100a** or **100d** by oxylactonization of alkenylbenzoates **99** with a lactate-based hypervalent iodine reagent generated *in situ* (Figure 11.25).

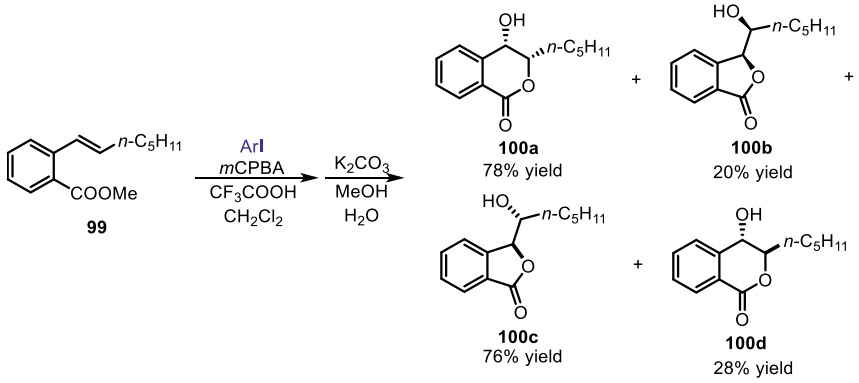


Figure 11.25: Synthesis of 4-hydroxyisochroman-1-ones via C(sp^2)–O bond formation mediated by I(III) generated *in situ*.

In 2020, Xiong's group [64] described a concise approach to access diverse polycyclic cyclohexadienones **103**, which could be used as potential inhibitors of DNA polymerase, from 3′-hydroxy-[1,1′-biphenyl]-2-carboxylic acids **101** through alkoxylactonization and dearomatization mediated by catalytic amount of chiral aryl-λ^3-iodane. Here the hypervalent iodine reagent was generated *in situ* from aryl iodine reagent **102** and *m*CPBA in alcohols (Figure 11.26).

In 2021, Du's group [65] reported that a series of alkoxylated isobenzofuranone compounds **105** could be synthesized from 2-(1-arylvinyl)benzoic acids **104** mediated by $PhI(OR)_2$, generated *in situ* from the reaction of PhIO with alkyl alcohols. This result implied that $PhI(OR)_2$ **106** could enable a cascade process encompassing lactonization with concomitant 1,2-aryl migration and alkoxylation. For the plausible mechanistic pathway, alcohols first reacted with PhIO to produce reactive $PhI(OR)_2$ **106**, which could activate the carbon–carbon double bond in substrates **104** to give the stable

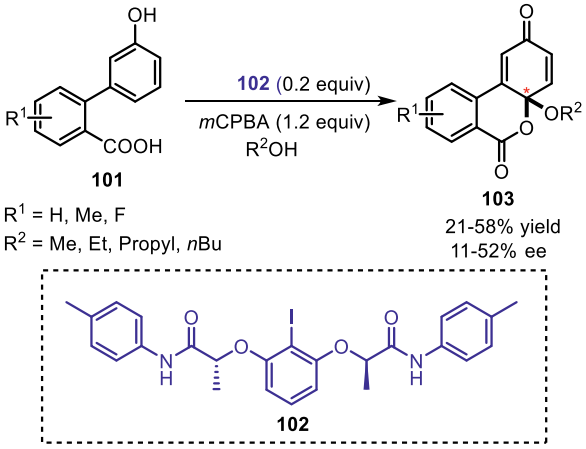
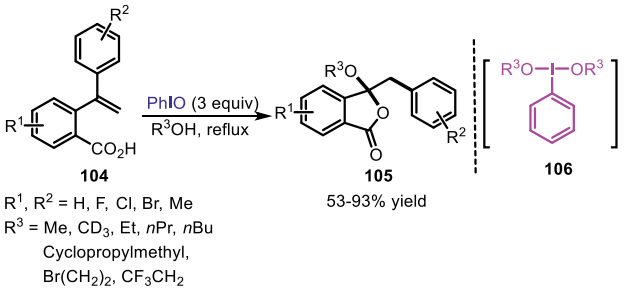


Figure 11.26: Synthesis of polycyclic cyclohexadienones via alkox-oxylactonization and dearomatization mediated by I(III) generated *in situ*.

benzhydryl carbocations **107**. Subsequently, the nucleophilic attack of the carbonyl oxygen in carboxylic acid moiety onto the carbocation led to the formation of oxonium ions **108**, which underwent deprotonation to deliver lactones **109**. Next, neighboring group participation of aryl group on the adjacent electron-deficient carbon attached to iodine(III) center occurred to afford the resonance stabilized carbonium ion intermediates **110**, with the concomitant loss of phenyl iodide and one molecule of methoxide. Then, the highly strained **110** was transformed into oxonium ion **111**, which realized the migration of phenyl group (from **109** to **111**). Finally, the capture of methoxide by the oxonium ion **111** led to formation of the title compound **105**. It is worth noting that the alkoxy group incorporated was from the corresponding alcohol, which was also used as a solvent for the reaction (Figure 11.27).

In 2019, Gong and colleagues [66] reported the conversion of allylic alcohols **112** to corresponding enantioenriched α-arylated β-alkoxylated ketones **114** through enantioselective alkoxylation/oxidative rearrangement mediated by the *in situ*-generated chiral hypervalent iodine reagent. In this reaction, substrates **112a** first reacted with BnOH to afford the alkoxylated intermediate **116a**. Next, intermediate **116a** reacted with TsOH and active chiral hypervalent iodine **115**, generated *in situ* from the oxidation of chiral organoiodine **113** with Selectfluor, to provide the iodine(III)-substrate complex **117**. Then, the carbon–carbon double bond of complex **117** was regioselectively and enantioselectively attack by water to form the crucial intermediate **118**. Subsequently, a semipinacol-type rearrangement occurred in intermediate **118**, resulting in the formation of intermediates **119** and one molecular of chiral organoiodine **113**, which entered back into the catalytic cycle. Finally, the title product **114a** was obtained through the deprotonation of intermediate **119** (Figure 11.28).



Plausible mechanistic pathway:

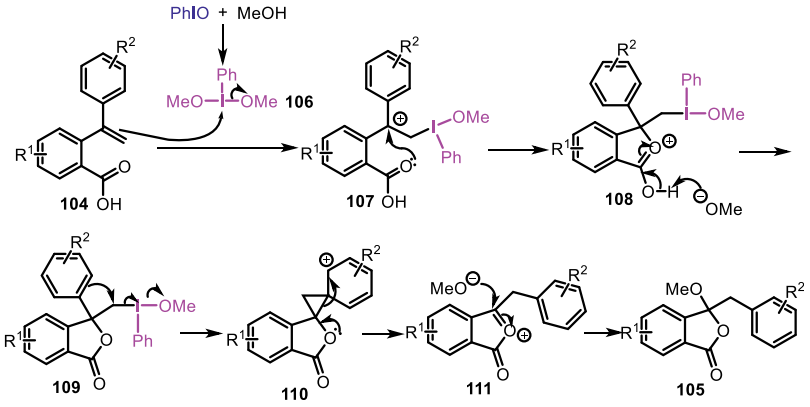


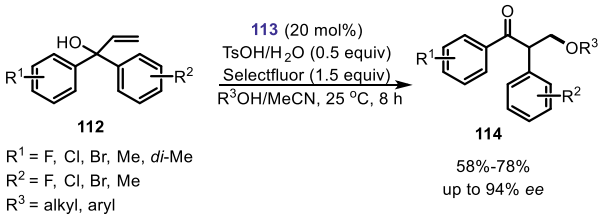
Figure 11.27: Synthesis of alkoxylated isobenzofuranones via lactonization, 1,2-aryl migration and alkoxylation mediated by I(III) generated *in situ*.

11.3.4 Heterocyclization

The oxazole skeleton could be found in many valuable natural products, and the development of novel methods for synthesizing such oxazoles has gained a great deal of attention from synthetic chemists. *In situ*-generated hypervalent iodine reagents have also found applications in the assemblage of oxazole skeletons.

In 2008, Togo's group [67] developed a one-pot manner for the preparation of 2-methyl-5-aryloxazole and 2-ethyl-5-aryloxazole derivatives **121** from alkyl aryl ketones **120** with iodoarene, *m*CPBA, and TfOH in acetonitrile and propionitrile, respectively. Here the catalyst iodoarene could react with *m*CPBA and TfOH to form *in situ* the reactive aryliodonium(III) species, which then reacted with enolate form of the substrates to construct the α-keto iodonium species **122**. Finally, intermediates **122** reacted with nitrile followed by release of TfOH to give the oxazoles (Figure 11.29).

In 2009, the same group [68] expanded the reaction by using different nitriles, including acetonitrile, propionitrile, butyronitrile, and isobutyronitrile, under similar conditions to



Plausible mechanistic pathway:

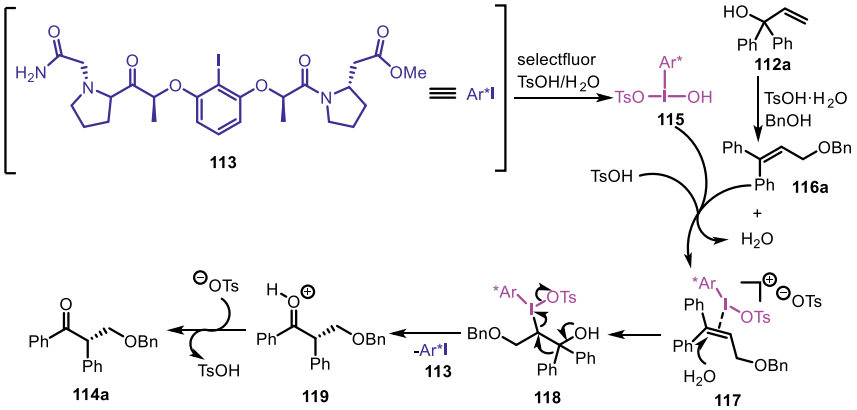
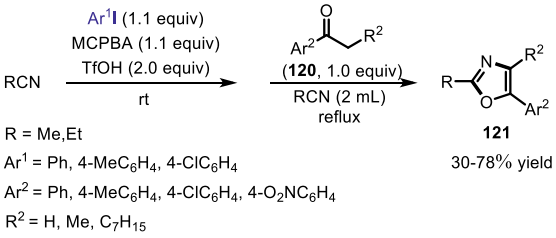


Figure 11.28: Synthesis of α-arylated β-alkoxylated ketones via enantioselective alkoxylation and oxidative rearrangement mediated by I(III) generated *in situ*.



Plausible mechanistic pathway:

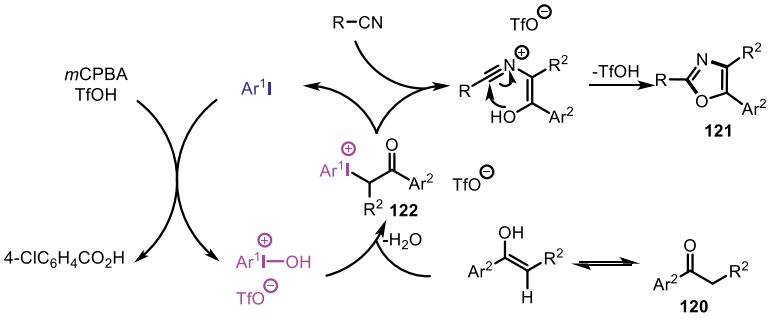


Figure 11.29: Synthesis of oxazoles via intermolecular cyclization mediated by I(III) generated *in situ*.

form 2-methyl-5-aryloxazoles, 2-ethyl-5-aryloxazoles, 2-propyl-5-aryloxazoles, 2-isopropyl-5-aryloxazoles, and 2,4-disubstituted 5-aryloxazoles, respectively. It was noted that *m*CPBA was replaced by inorganic and much cheaper oxone in this reaction (Figure 11.30).

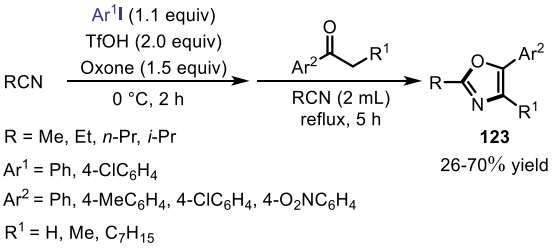


Figure 11.30: Synthesis of oxazoles via intermolecular cyclization mediated by I(III) generated *in situ*.

At the same time, Togo's group [69] further investigated the similar transformation from ketones to oxazoles. Diverse oxazoles were smoothly and efficiently synthesized with moderate yields through the reaction of alkyl aryl ketones and the *in situ*-generated hypervalent iodine compound, formed from iodoarene and *m*CPBA in the presence of TfOH. Notably, IL-supported PhI, which has the advantages of low vapor pressure, low flammability, high thermal stability, easy reusability, and easy separation, could also be used as catalyst for the preparation of oxazoles (Figure 11.31).

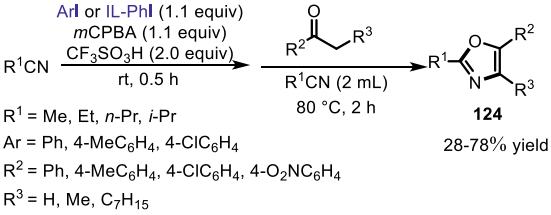


Figure 11.31: Synthesis of oxazoles via intermolecular cyclization mediated by I(III) generated *in situ*.

In 2013, Yoshimura and coworkers [70] found that the reaction of aldoximes **125** with the *in situ*-generated iodine(III) reagent, formed from oxone and iodoarene in aqueous MeOH solution in the presence of HFIP, could deliver nitrile oxide intermediate, which were then cycloadded with alkenes and alkynes to produce the corresponding isoxazolines **126** and isoxazoles **127**, respectively. According the result, HFIP could accelerate the reaction rate of catalytic cycle by promoting ligand exchange and oxidation of aldoxime (Figure 11.32).

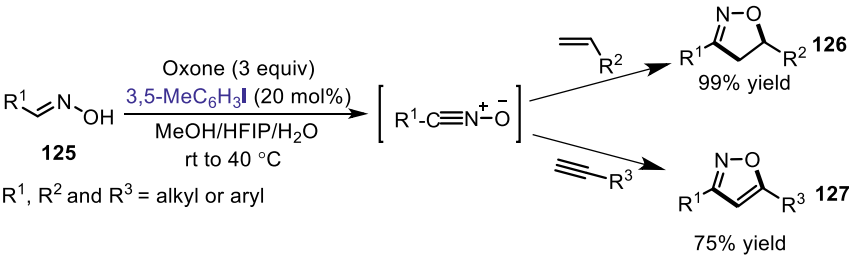


Figure 11.32: Synthesis of isoxazoles and isoxazolines through oxidation mediated by I(III) generated *in situ*.

In 2015, Moran and research fellows [71] reported that the biologically interesting oxazoles **129** could be prepared from *N*-alkenylamides **128** via cyclization mediated by hypervalent iodine(III) reagents generated *in situ* from iodoarenes. The olefin on substrates **128** was first activated by iodine(III) species and then attacked by the amide oxygen to form intermediates **130**. After that, intermediates **130** captured one molecule of TFA to break the C–I bond, leading the formation of cyclized products **129**. Notably, the enantioselectivity of the products was controlled by chiral iodoarene precatalysts at the level of 81:19 *er* (Figure 11.33).

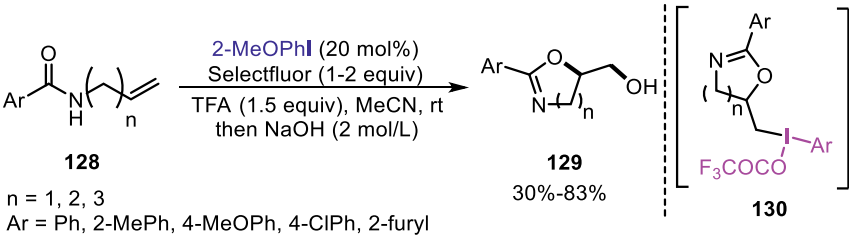
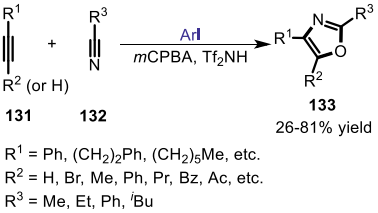


Figure 11.33: Synthesis of oxazoles through cyclization mediated by I(III) generated *in situ*.

In 2017, Saito and coworkers [72] reported a regioselective [2+2+1]-type cycloaddition between alkynes **131** and nitriles **132** for the preparation of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles products **133** under metal-free conditions. In this conversion, the $PhI(OH)NTf_2$ catalyst, *in situ* generated from iodoarene as a precatalyst with *m*CPBA and Tf_2NH, could react with the triple bond of alkynes **131** by iodoimidation and followed by ligand exchange of OH group in intermediates **134** to afford intermediate **135**. Next, the nucleophilic vinylic substitution at the β-position of reactive intermediates **135** by R^3CN occurred to produce intermediates *trans*-**136**. After repeated addition and elimination of R^3CN, intermediates *trans*-**136** were transformed into *cis*-**136**. Subsequently, intermediates *cis*-**137** and **138** were formed from *cis*-**136** by the ligand exchange of NTf_2 group and the addition to ammonium ion with H_2O. Finally, intermediates **137** and **138** would undergo cyclization followed by reductive elimination to give title products **133** and regenerate iodine catalyst. Another possible pathway was that intermediates *trans*-**136** or **137** could afford intermediate *cis*-**140** through the nucleophilic vinylic substitution at the *α*-position of *trans*-**136** with H_2O or the ligand coupling of *trans*-**137** followed by keto-enol tautomerization. Finally, the target products **133** were obtained from intermediates *cis*-**140** via intramolecular cyclization (Figure 11.34).



Proposed mechanistic pathway:

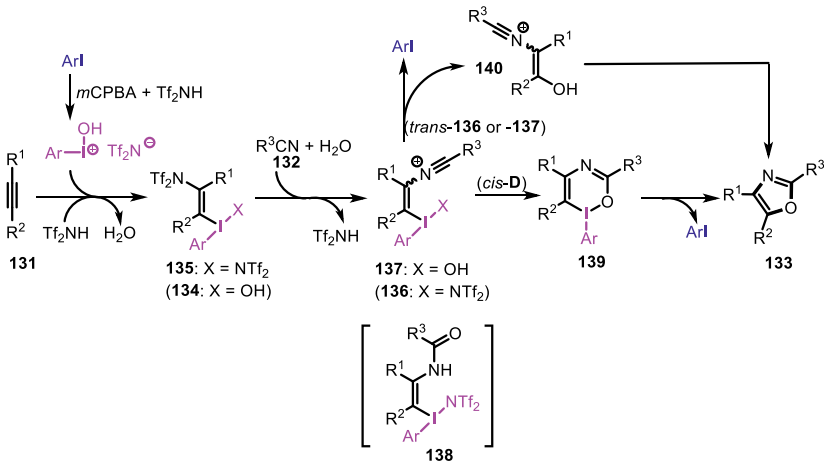


Figure 11.34: Synthesis of oxazoles through [2+2+1] cycloaddition mediated by I(III) generated *in situ*.

In 2017, Moran and Kamouka [73] reported an intramolecular cyclization of *N*-propargylamides and β-amidoketones meditated by the *in situ*-generated hypervalent iodine species, affording 2-oxazolines **145** in yield of 35–95%. Two complementary routes were proposed, with alkyne or enolate activated by the *in situ*-formed hypervalent iodine(III), which was generated from oxidation of 2-iodoanisole by *m*CPBA. Finally, intramolecular cyclization occurred to produce the target products **145** (Figure 11.35).

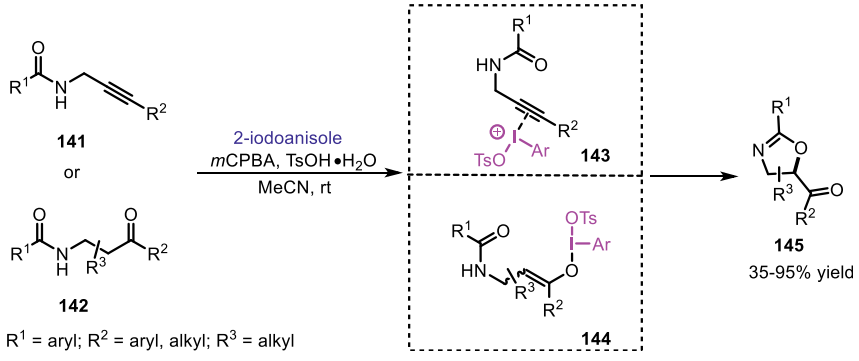


Figure 11.35: Synthesis of oxazolines through cyclization mediated by I(III) generated *in situ*.

In 2019, Moran and coworkers [74] explored the reaction rate and mechanism for the synthesis of trifluoroacetylated 4,5-dihydrooxazole **147** from *N*-allylbenzamide **146** in presence of diverse iodoarenes and Selectfluor/TFA system. The oxidant was an iodine(III) compounds, i.e., $ArIF_2$ or $ArI(CF_3CO_2)_2$ formed *in situ*. The formed hypervalent iodine species reacted with *N*-allylbenzamide **146** to form 4,5-dihydrooxazole intermediates **148**, which would be then trifluoroacetylated with TFA to give the target products **147** (Figure 11.36).

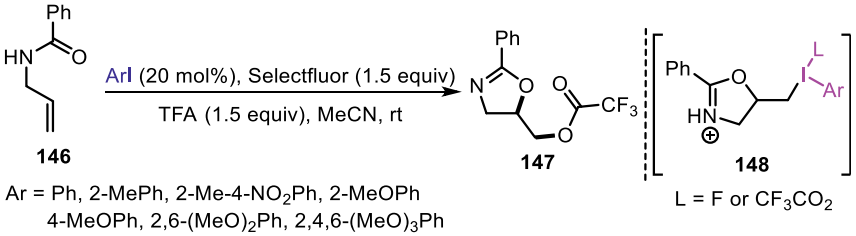


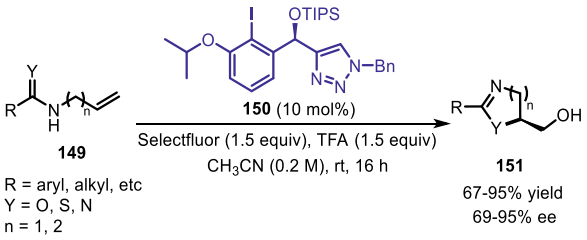
Figure 11.36: Synthesis of oxazoline through heterocyclization/acyloxylation mediated by I(III) generated *in situ*.

In 2021, Nachtsheim's group [75] found that the enantioselective oxidative cyclization of *N*-allyl carboxamides **149** could occur by chiral triazole-substituted iodoarene catalyst. A series of 5-oxazolines, thiazolines, and imidazolines were obtained with high yield and high enantioselectivity by the method. The proposed mechanism for this reaction involves the *in-situ* formation of hypervalent iodine reagents from iodoarene and Selectfluor. After activating of carbon–carbon double bond by active iodine(III), *N*-allyl carboxamides **149** was then attacked by the intramolecular amide oxygen to give alkyl-substituted iodanes **153**. Subsequently, the Brønsted acids TFA could rapidly reduce the alkyl-substituted iodanes **153** to afford intermediates **154** and precatalyst **150**. Finally, intermediates **154** would react with nucleophilic H_2O to form the substituted oxazolines **151** (Figure 11.37).

In recent years, the construction of oxazole skeleton with the concomitant introduction of fluorine atoms via fluorocyclization of unsaturated compounds mediated by the *in situ*-generated hypervalent iodine species has been extensively studied.

In 2016, Saito's group [76] reported that *N*-propargyl amides **155** could react with iodine(III) catalyst, undergoing cyclo-isomerization–fluorination sequence to afford fluoro-containing oxazoles **156** in moderate yields. Here the active hypervalent iodine species was generated *in situ* from the precatalyst iodoarene with fluorinating oxidant Selectfluor in the presence of HF·pyridine (Figure 11.38).

In 2018, Gilmour's group [77] demonstrated a convenient process for the catalytic fluorooxygenation of readily accessible *N*-allylcarboxamides **157** using *p*-iodotoluene (*p*-TolI) as the precatalyst in the presence of Selectfluor and HF. Here the reactive *p*-$TolIF_2$ was formed *in situ*, and the HF was both a fluoride source and Brønsted acid activator (Figure 11.39). In 2019, by using electrochemistry, Waldvogel and coworkers



Plausible mechanistic pathway:

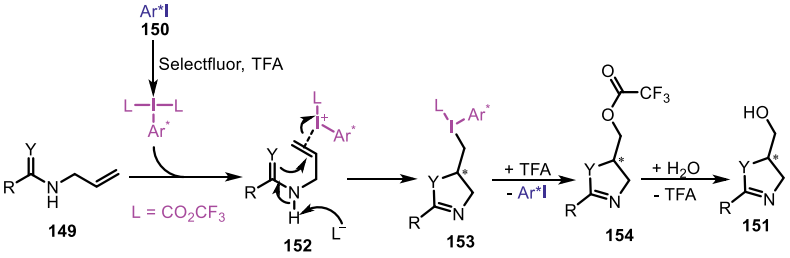


Figure 11.37: Synthesis of 5-oxazolines, thiazolines, and imidazolines via C(sp^2)–O bond formation mediated by I(III) generated *in situ*.

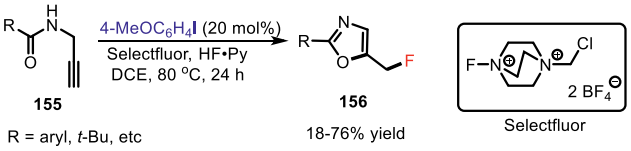


Figure 11.38: Synthesis of fluoro containing oxazoles via cyclo-isomerization–fluorination mediated by I(III) generated *in situ*.

[78] also realized the fluorocyclization of *N*-allylcarboxamides **157**, providing a resource saving method for the synthesis of 5-fluoromethyl-2-oxazolines **158**. Sixteen kinds of substrates were examined by this method, and the yield was as high as 68% (Figure 11.39).

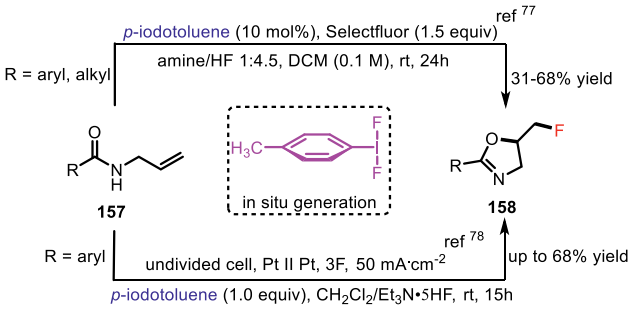


Figure 11.39: Synthesis of fluoro containing 2-oxazolines via fluorooxygenation mediated by I(III) generated *in situ*.

In 2019, Waldvogel's group [79] reported a green alternative electrochemical method over conventional reagent-based approaches for the synthesis of 5-fluoromethyl-2-oxazoles **160**. In this conversion, the hypervalent oxidant, i.e., $ArIF_2$ was generated *in situ* by electrochemical oxidation of ArI in the presence of $Et_3N{\cdot}5HF$. A variety of *N*-propargylamides **159** could react smoothly to give the corresponding fluorinated oxazoles **160** with yields up to 65% (Figure 11.40).

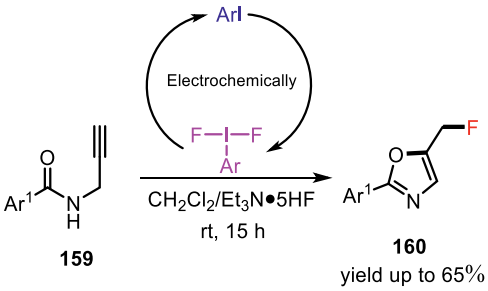


Figure 11.40: Synthesis of oxazoles involving a fluoromethyl group via fluorocyclization mediated by I(III) generated *in situ*.

In 2020, Saito's group [80] illustrated an organoiodine-catalyzed method for the preparation of fluorine-containing oxazoles **163** by fluorocyclization of *N*-propargyl carboxamides **161**. In this transformation, iodoarenes **162** initially reacted with Selectfluor and HF·pyridine to *in situ* generate the reactive fluoro-λ^3-iodane(III) species, which would activate the triple bond of *N*-propargyl carboxamides **161** to form cyclized intermediates **165**. Subsequently, aromatization of intermediates **165** could occur to produce intermediates **167**. Finally, intermediates **167** were further converted to the title products **163** with elimination of the precatalyst **162**, which entered back into the catalytic cycle (Figure 11.41).

Proposed mechanistic pathway:

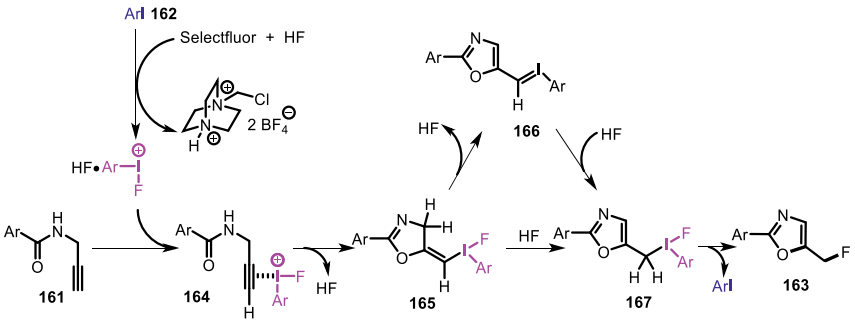
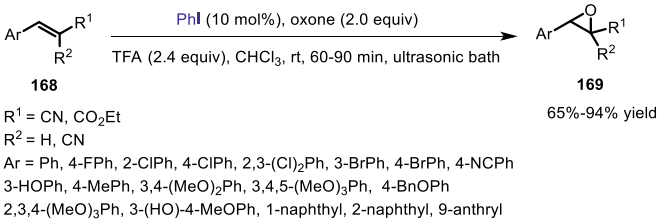


Figure 11.41: Synthesis of oxazoles involving a fluoromethyl group via fluorocyclization mediated by I(III) generated *in situ*.

11.3.5 Epoxidation of alkenes

In the history of synthetic and pharmaceutical chemistry, β-cyanoepoxide scaffolds have been considered to be important organic molecules. In 2019, Mangaonkar and Singh [81] demonstrated an efficient method to synthesize β-cyanoepoxides **169** through an iodine(III)-mediated epoxidation of electron deficient β-cyanostyrenes **168** under transition metal-free reaction conditions. For reaction process, it was postulated that the oxidation of PhI was first realized by oxone and TFA under ultrasonic radiation, which led to the formation of active iodine(III) species *in situ*. Then the iodine(III) species activated the double bond of substrates **168** to afford the three-membered iodonium intermediates **170**. Next, the trifluoroacetoxy anion nucleophilically attacked on the three-membered iodonium to form intermediates **171**, and finally the desired products **169** was obtained via intramolecular cyclization, with the release of PhI (Figure 11.42).



Proposed mechanistic pathway:

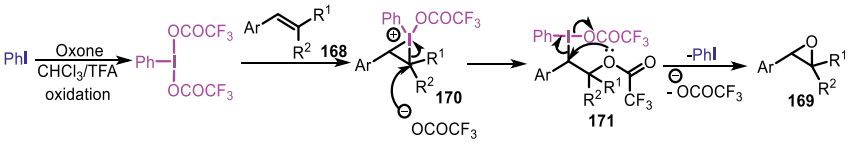


Figure 11.42: Synthesis of β-cyanoepoxides through epoxidation mediated by I(III) generated *in situ*.

11.3.6 Acetoxylation

In 2005, Ochiai's group [82] disclosed that α-acetoxylation could occur when ketones **172** were treated with $PhI(OAc)_2$, which was formed *in situ* from the reaction of catalytic amount of PhI with *m*CPBA in the presence of acetic acid. Interestingly, the addition of $BF_3{\cdot}Et_2O$ and water could accelerate the oxidation of PhI to $PhI(OAc)_2$, and the α-acetoxylation of ketones, respectively (Figure 11.43).

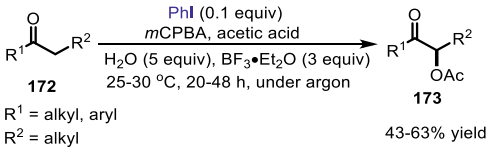


Figure 11.43: Synthesis of α-acetoxy ketone through α-acetoxylation mediated by I(III) generated *in situ*.

In 2020, Wirth's group [83] reported a method for synthesis of α-acetoxylated ketones **176** by treating enol ethers **174** with hypervalent iodine species, which was generated *in situ* from the oxidation of resorcinol/lactamide-based chiral iodoarene by *m*CPBA in the presence of $BF_3{\cdot}Et_2O$ (Figure 11.44).

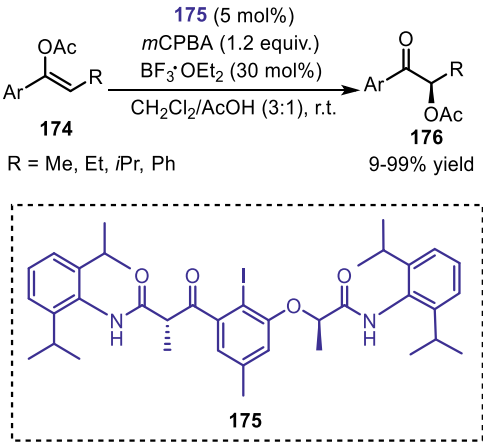


Figure 11.44: Synthesis of α-acetoxylated ketones via C(sp^2)–O bond formation mediated by I(III) generated *in situ*.

11.3.7 *Syn* diacetoxylation of alkenes

In 2012, Meng, Li and coworkers [84] applied the metal-free *syn* diacetoxylation of alkenes **177** using organoiodine(III) catalysts to synthesize the *syn* diacetates **178** in good to excellent yields and high diastereoselectivity. The organoiodine(III) catalysts were formed *in situ* from the reaction of the readily available aryl iodide catalysts and cheaper oxidants. It is worth noting that both electron-rich and electron-deficient alkenes were well compatible under the reaction conditions (Figure 11.45).

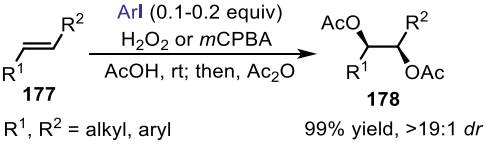
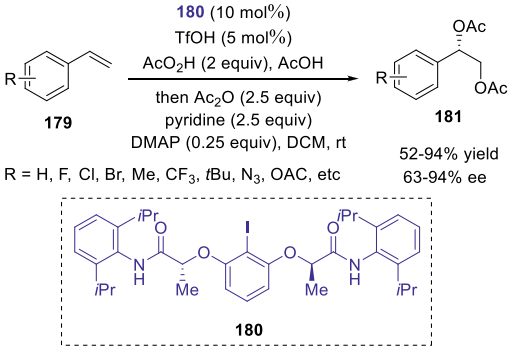


Figure 11.45: Synthesis of *syn* diacetates through *syn* diacetoxylation mediated by I(III) generated *in situ*.

In 2016, Muniz's group [85] realized the synthesis of vicinal diacetoxylated products **181** from the reaction between different alkenes **179** and *in-situ* formed chiral nonracemic hypervalent iodine(III) reagents. The mechanistic pathway of this enantioselective deoxygenation process was postulated as follows. Initially, chiral iodoarene reacted with AcO_2H in AcOH at room temperature to afford the active intermediate **182a**, which possessed a hydrogen bonding to form a cyclic stereochemical arrangement. Then TfOH would dissociate one acetate group to provide the iodine(III) intermediate **182b**. Next, the exposed *re*-face of coordination complexes of iodine(III) with alkenes were nucleophilically attacked by acetate to give intermediates **183**. Subsequently, intermediates **183** were converted to dioxolane intermediates **185** via

intramolecular nucleophilic addition of the acetate, together with elimination of the chiral aryl iodine which entered back into the next catalytic cycle. Last, the nucleophilic addition of water to intermediates **185** produced two regioisomeric acetoxy alcohols **186a** and **186b**, which then reacted with acetic anhydride to form the target products **181** (Figure 11.46).



Proposed mechanistic pathway:

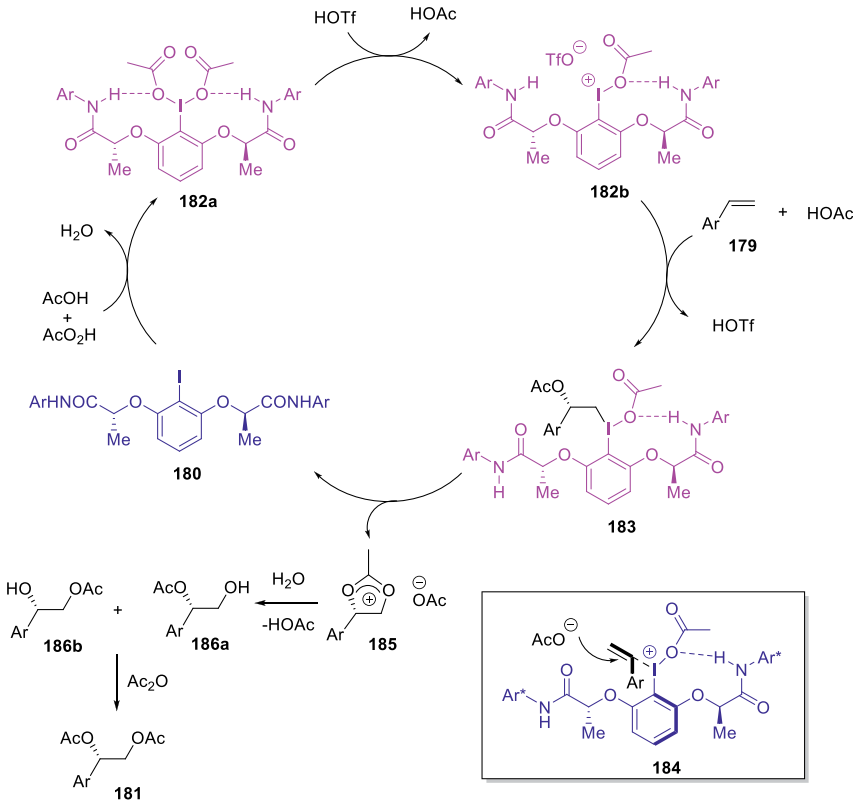
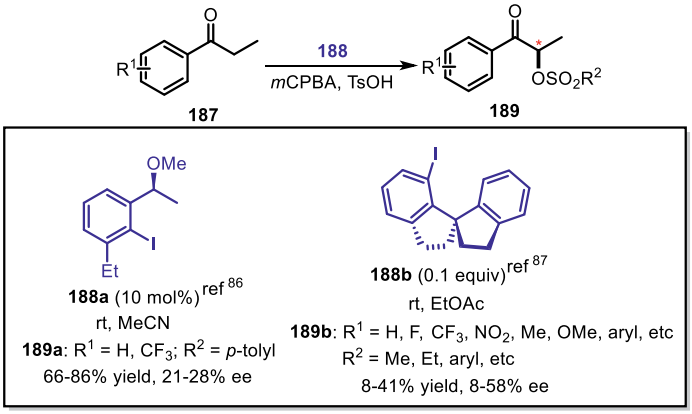


Figure 11.46: Synthesis of vicinal diacetoxylation products through enantioselective deoxygenation mediated by I(III) generated *in situ*.

11.3.8 α-tosyloxylation

In 2008, Wirth's group [86] developed an *in situ*-generated iodine(III) reagent-promoted α-oxysulfonylation of ketone derivatives **187**, the reaction of which gave the corresponding α-tosyloxylated ketones **189** in good yields and moderate enantioselectivity. Mechanistically, the reaction initialized from enantio-enriched iodoarenes and *m*CPBA to give Koser-type iodane. For path **A**, the ketone substrates reacted with Koser-type iodane through ligand exchange to give intermediates **190**, which were attacked by tosylate to give the target products **189** and precatalyst **188a**. For path **B**, the iodine center of hypervalent iodine species would be attacked by the double-bond electrons of the ketone substrates to form intermediates **191**, which underwent S_N2-type replacement by the tosylate to give α-tosyloxylated ketones **189** (Figure 11.47). In 2011, Zhang's group [87] successfully synthesized a new class of chiral iodoarenes **188b** with rigid spirobiindane backbones and have them utilized in α-tosyloxylation of ketones **187**, which afforded a wide range of useful α-tosyloxylated ketones **189b** with *ee* value up to 58%. In this method, *p*-TsOH·H_2O was used as the source of the tosylate nucleophile. Interestingly, when different sulfonic acids were applied, asymmetric α-sulfoxylation could occur under the same reaction conditions to generate the corresponding sulfonyloxylated product (Figure 11.47).



Plausible mechanistic pathway:

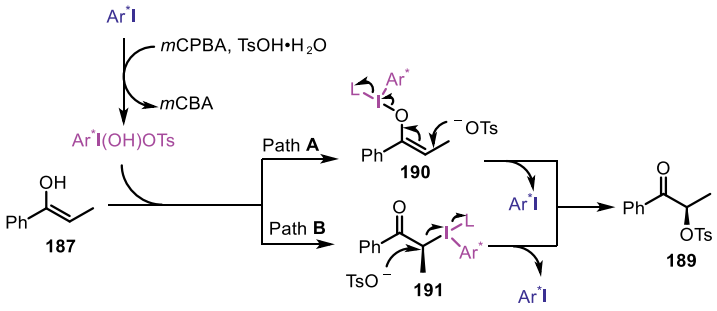
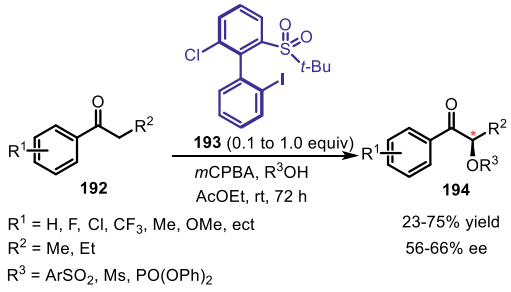


Figure 11.47: Synthesis of α-tosyloxylated ketones via C(sp^2)–O bond formation mediated by I(III) generated *in situ*.

In 2017, Masson's group [88] reported an enantioselective direct oxygenation of propiophenone derivatives **192** by treatment with a chiral hypervalent iodine species generated *in situ* from chiral non C_2-symmetric iodoarenes **193**, *m*CPBA and sulfonic acid or diphenyl phosphate. Diverse α-oxygenated ketones bearing different substituents **194** were obtained through oxidative C–O bond formation in satisfactory yields and enantioselectivies. Mechanistically, the reaction of propiophenones and aryl-λ^3-iodane(III) agents underwent two potential pathways to form α-oxygenated ketones. In path A, *O*-enolate (O–I–Ar*) intermediates **195** could be obtained from substrates **192** by ligand exchange and subsequent reacting with oxygenated nucleophile. The title products **194** were obtained through a S_N2'-type nucleophilic substitution of **196**, with the regeneration of precatalyst **193**. Path B involved the nucleophilic addition of oxygenated nucleophile upon the C–I–Ar* **197**, resulting in the formation of target products **194** and chiral iodoarene **193** (Figure 11.48).



Plausible mechanistic pathway:

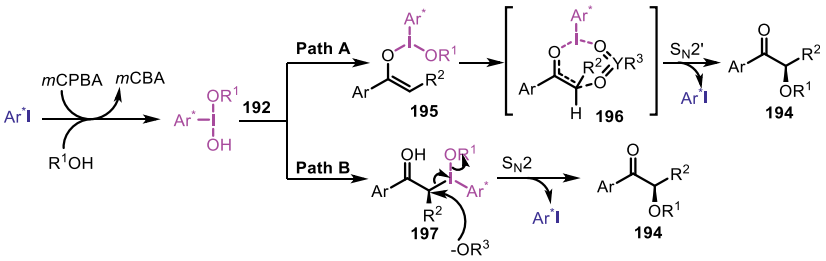


Figure 11.48: Synthesis of α-sulfonyl and α-phosphoryl oxyketones via oxygenation mediated by chiral I(III) generated *in situ*.

In 2016, Xiong, Coeffard et al. [89] disclosed that asymmetric α-oxidation of β-keto esters containing a stereogenic center could occur in the presence of the *in situ*-formed chiral hypervalent iodine agent. Notably, in addition to different α-substituted β-keto esters, other arylsulfonic acids **198** could also tolerate this reaction conditions and proceed smoothly to give target products **200** with moderate yield (Figure 11.49).

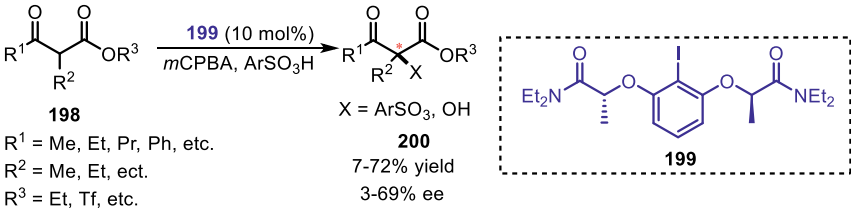


Figure 11.49: Synthesis of oxygenated-β-keto esters via asymmetric oxidation mediated by chiral I(III) generated *in situ*.

In 2021, Wirth's group [90] realized the same oxygenative reaction of ketone derivatives **201** with chiral hypervalent iodine reagent, which was generated *in situ* from the C–N axially chiral iodoarenes and *m*CPBA in the presence of TsOH, affording the corresponding α-oxygenated products **203** in good to excellent yields. The novel C–N axially chiral iodoarenes **202** was obtained from commercially available aniline derivatives in a three-step (Figure 11.50).

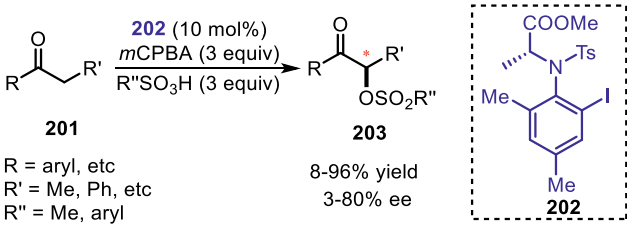


Figure 11.50: Synthesis of α-oxygenated products via stereoselective α-oxytosylation mediated by chiral I(III) generated *in situ*.

In 2015, Whitehead's group [91] discovered a series of peptide-based iodoarene catalysts and applied them in a α-oxytosylation of some substituted propiophenones, affording the corresponding α-tosyloxy ketone products **206** with good to excellent yields. The reactive hypervalent iodine reagents were generated *in situ* from the oxidation of iodoarenes by *m*CPBA in the presence of *p*TSA·H_2O (Figure 11.51).

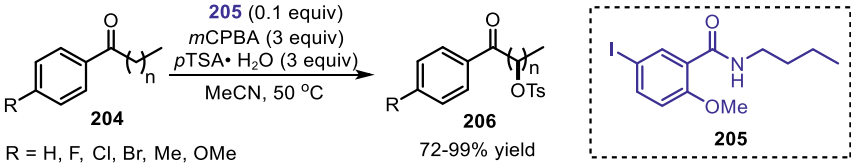


Figure 11.51: Synthesis of α-tosyloxy ketones through α-oxytosylation mediated by I(III) generated *in situ*.

In 2019, Boelke and Nachtsheim [92] realized a α-tosyloxylation of ketones **207** mediated by hypervalent iodine(III) reagent generated *in situ*, leading to the formation of *α*-tosyloxylated ketones **209**. It is worth noting that the loading of organocatalysts *N*-heterocycle-substituted iodoarenes (NHIAs) **208** was the lowest, as only 1 mol% of NHIAs **208** could ensure an efficient reaction (Figure 11.52).

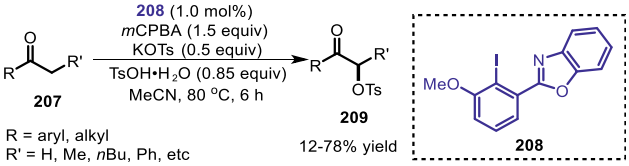
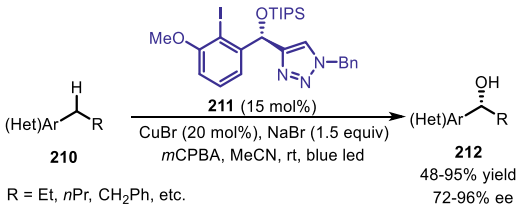


Figure 11.52: Synthesis of α-tosyloxylated ketones through α-tosyloxylation mediated by I(III) generated *in situ*.

11.3.9 Hydroxylation

The direct hydroxylation of benzylic C(sp^3)–H mediated by the *in situ*-generated hypervalent iodine species emerged to be a promising organic transformation. In 2020, Nachtsheim and coworkers [93] reported a triazole-substituted chiral iodoarene-catalyzed enantioconvergent hydroxylation of alkyl arenes **210**, affording the chiral benzyl alcohols **212** in high selectivity with moderate to excellent yields. The results showed that the substrates with electron-rich, electron-poor, exocyclic π-bonds, or *N*-heterocycles groups could be all well converted to the desired products with good yields. Mechanistically, iodoarene **211** was oxidized by *m*CPBA to form hydroxy(aryl)-λ^3-iodane(III) **213**, which was further converted to bromo(aryl)-λ^3-iodane(III) **214** through ligand exchange with NaBr. Under irradiation, intermediated **214** underwent homolytic cleavage of the labile I–Br bond, resulting in the formation of bromine radical and the radical cation **215**. Next, the benzylic C–H bonds could be activated by bromine radical to afford benzyl bromides **216**. At the same time, the obtained hydroxy(aryl)-λ^3-iodane(III) **213** could hydroxylate the Cu salt to give the active chiral Cu-hydroxy complex **217** under dark conditions. Finally, under the mediation of the active chiral Cu-hydroxy complex **217**, benzyl bromides **216** could be converted to the chiral benzyl alcohols **212**, along with the regeneration of precatalysts **211**. Here the chiral aryl iodide catalyst not only worked as an oxidant in the radical bromination, but also acted as a chiral ligand in the Cu-catalyzed step (Figure 11.53).

In 2009, Quideau's group [94] discovered that the *in situ*-formed hypervalent iodine reagent could mediate asymmetric hydroxylative dearomatization of phenols. Treatment of naphthol **218** with two-fold excess of axial chiral binaphthyl iodoarene **219** in presence of *m*CPBA could afford the *ortho*-quinol **220** in a good yield and 50% *ee* value. Furthermore, using only a catalytic amount of chiral iodoarenes **221**, naphthol **218** could be transformed into epoxide compounds **222** with excellent yield but lower *ee* value (Figure 11.54).



Plausible mechanistic pathway:

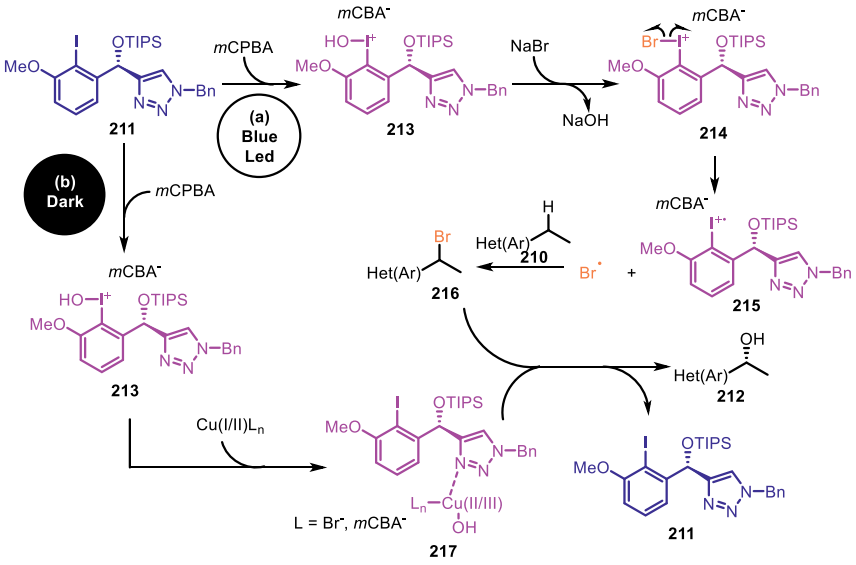


Figure 11.53: Synthesis of chiral benzyl alcohol through enantioselective hydroxylation mediated by I(III) generated *in situ*.

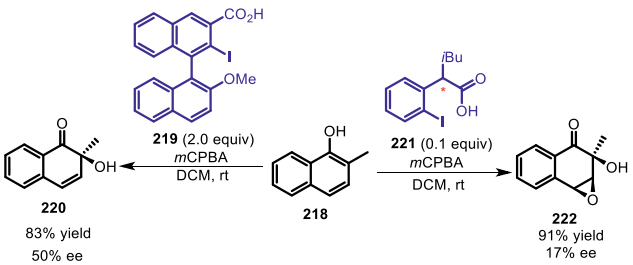


Figure 11.54: Synthesis of chiral alcohol through asymmetric α-hydroxylation mediated by chiral I(III) generated *in situ*.

11.4 Formation of carbon–nitrogen bond

Recent years have witnessed a rapid development of strategies for the synthesis of nitrogenous compounds due to their abundance in numerous natural products, pharmaceuticals, functional materials, and organic synthetic intermediates. The related transformations mediated by the *in situ*-generated hypervalent iodine reagents were summarized as follows.

11.4.1 Aza-spirocyclization

Strategies to construct pharmaceutically interesting spirocyclic skeletons from phenol derivatives mediated by the *in situ*-generated hypervalent iodine species have been extensively explored in organic chemistry. A series of organoiodine catalyzed dearomatization reaction have been reported to realize aza-spirocyclization.

In 2007, Kita and coworkers [95] reported the synthesis of N-fused spirolactams **224a** through spirocyclization of functionalized amides **223** mediated by iodotoluene and *m*CPBA in 2,2,2-trifluoroethanol (TFE). Notably, this transformation involved the generation of the active hypervalent iodine species **225** *in situ*. Most strikingly, it was the first example of using iodoarene as the catalyst to construct the C–N bond. Then, in 2010, the same group [96] found that the *in situ*-formed μ-oxo bridged heterocyclic hypervalent iodine reagents **226** could mediate dearomatization cyclization of amides **223** to construct the spiro C–N bond. Here iodine(III) compounds **226** were derived from iodotoluene and peracetic acid (PAA). Specifically, the halogenated aryl propenamide could also give the corresponding spirolactams with excellent yield (Figure 11.55).

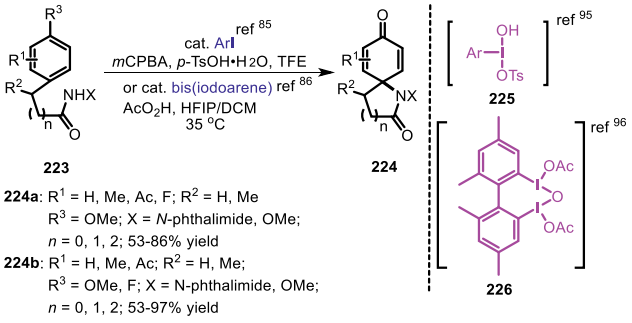
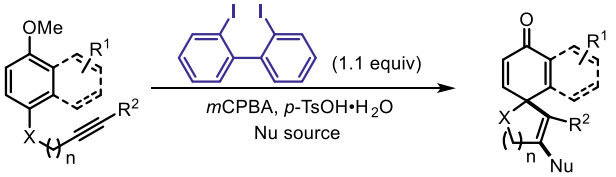


Figure 11.55: Synthesis of *N*-fused spirocycles via oxidative spirocyclization mediated by I(III) generated *in situ*.

Later, Kita's group [97] further discovered that the reaction of arylalkynes **227** with the *in situ*-generated hypervalent iodine species could undergo intramolecular cyclization to produce spirocyclic compounds **228** with moderate to excellent yields. It was worth noting that the nucleophiles could be installed to produce functionalized



227

228

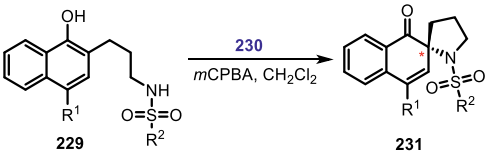
60%-99% yield

R^1 = H, Cl, OMe, ^{t}Bu
R^2 = Ph, Br, 4-anisyl
n = 0, 1, 2; X = NHCO, OCO, C
Nu = N_3, NO_2, SCN, SO_2Tol, Br

Figure 11.56: Synthesis of varied functionalized spirocyclic compounds through spirocyclization mediated by I(III) generated *in situ*.

spirocyclic compounds, which were difficult to be obtained with previous spirocyclization methods (Figure 11.56).

In 2019, Ciufolini, Hein et al. [98] established an enantioselective oxidative cyclization approach for synthesizing spirocyclic compounds **231** from 1-naphtholic sulfonamides **229**, induced by the *in situ*-generated chiral hypervalent iodine(III). Although the *ee* values of the products were moderate, the recrystallization could increase their ee to >99% (Figure 11.57).

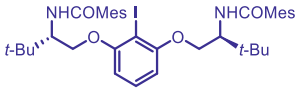


229

231

R^1 = alkyl, aryl
R^2 = H, aryl, halide

13%-45%
(ee: up to 67%)



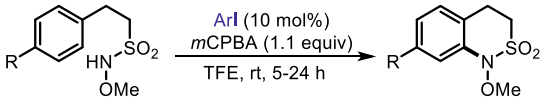
230

Figure 11.57: Enantioselective synthesis of spirocyclic compounds through enantioselective cyclization mediated by chiral I(III) generated *in situ*.

11.4.2 *N*-heterocyclization

Development of novel methods for the preparation of N-containing heterocyclic compounds through intramolecular C–H amination mediated by *in situ*-generated hypervalent iodine reagents have been well studied.

In 2009, Togo and Ishiwata [99] provided a straightforward method to synthesize *N*-methoxy-3,4-dihydro-2,1-benzothiazine-2,2-dioxides **233** from *N*-methoxy-2-arylethanesulfonamides **232** via an intramolecular cyclization. Here the oxidative iodine(III) species, was *in situ*-generated from ion-supported PhI and *m*CPBA in the presence of TFE (Figure 11.58).



232

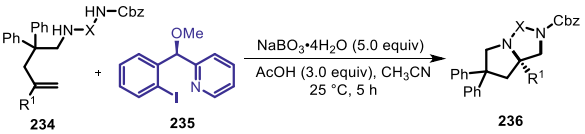
R = H, Me, F, Cl, Br, $ClCH_2$

233

31%-93% yield

Figure 11.58: Synthesis of benzothiazine via intramolecular cyclization mediated by I(III) generated *in situ*.

In 2014, Wirth and coworkers [100] reported a stereoselective intramolecular diamination of alkene derivatives **234** by the *in situ*-formed chiral hypervalent iodine species, affording the bicyclic products **236** in 45–72% yield. The chiral hypervalent iodine species was generated *in situ* from the novel chiral iodoarene **235** and $NaBO_3$, which was used as the terminal oxidant (Figure 11.59).



234

235

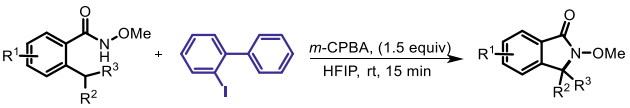
R^1 = H, Me
X = SO_2, NTs, NCbz

236

45-72% yield
76-86% ee

Figure 11.59: Synthesis of bicyclic compounds via oxidative bicyclization mediated by chiral I(III) generated *in situ*.

In 2015, Shi, Houk and coworkers [101] used iodoarene and *m*CPBA to *in situ* generate hypervalent iodine species, which could induce the conversion of *N*-methoxyl amide derivatives **237** to the amination products **238** via intramolecular amination. The yield of these products could reached 95%. Especially, the chiral quaternary centers could be constructed through this amination (Figure 11.60).



237

R^1 = alkyl, alkoxyl, halide
R^2, R^3 = alkyl groups

238

up to 95%

Figure 11.60: Synthesis of lactams via amination mediated by I(III) generated *in situ*.

In 2018, Mal and coworkers [102] succeeded in realizing oxidative C–N bond coupling of biarylsulfonailides **239** by using the *in situ*-generated iodine(III) species via *meta*-C–H bond functionalization. The corresponding carbazoles **240** were achieved in yield up to 98%. The active iodine(III) species was formed *in situ* by the PhI-*m*CPBA system (Figure 11.61).

In 2018, Cai and co-workers [103] realized the synthesis of lactams or spirolactams **242** from variously substituted amides **241** via an asymmetric oxidative C–N bond formation/catalytic desymmetrization process mediated chiral hypervalent iodine

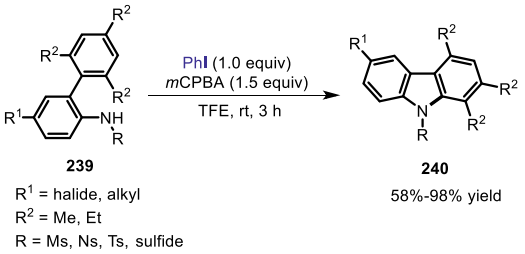


Figure 11.61: Synthesis of carbazoles through oxidative monocyclization mediated by I(III) generated *in situ*.

species, generated *in situ* from catalytic amount of chiral diiodospirobiindane derivative and stoichiometric *m*CPBA. Products were obtained in 50–88% yield with moderate to good enantioselectivities (Figure 11.62).

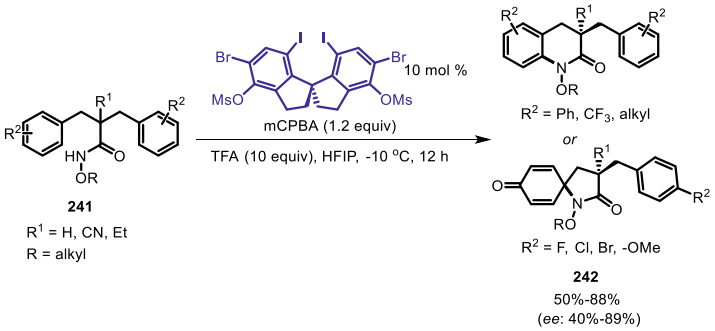


Figure 11.62: Synthesis of lactams or spirolactams via asymmetric cyclization mediated by chiral I(III) generated *in situ*.

In 2018, Jacobsen and his colleagues [104] developed a catalytic enantioselective fluorofunctionalization reaction to convert alkenes **243** to the *syn*-*β*-fluoroaziridines **245** in moderate to excellent yield with moderate to good *ee* values. In this transformation, HF-pyridine was employed as a nucleophilic fluoride and the chiral hypervalent iodine was oxidative species, which was generated *in situ* by the oxidation of chiral aryl iodine **244** by *m*CPBA. The *anti*-*β*-fluoropyrrolidines and 1,2-oxyfluorinated compounds could also be obtained under the same conditions (Figure 11.63).

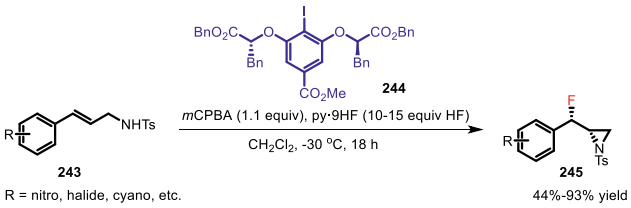


Figure 11.63: Synthesis of aziridines via diastereoselective fluoroamination mediated by chiral I(III) generated *in situ*.

In 2020, Power's group [105] realized the catalytic use of chiral hypervalent iodine species, generated from the corresponding aryl iodide **247a** or **247b** in the presence of hflip, [TBA]PF_6 and [TBA]OAc utilizing an electrochemical strategy. Under constant potential electrolytic conditions, aryl acetamides **246** and hydrazine derivative **249** were converted into C–N coupled products **248** and **251**, respectively. The key intermediate iodanyl radical could be critically stabilized by adding acetate ions (Figure 11.64).

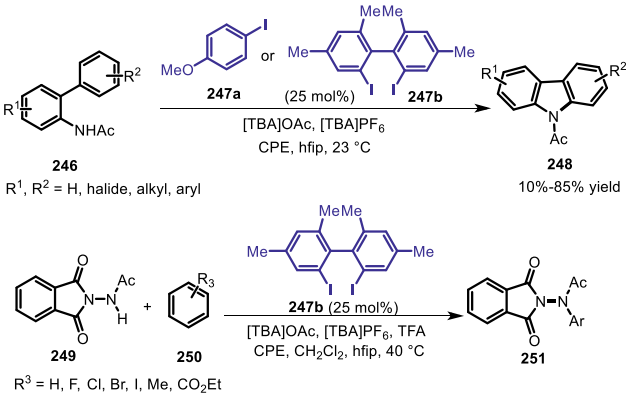


Figure 11.64: Synthesis of carbazoles and *N*-phenylated compounds via intra- and intermolecular C–H/N–H coupling reactions mediated by I(III) generated *in situ*.

In 2020, Driver's group [106] realized the conversion of inactivated 2-substituted anilines **252** to the bioactively important nonplanar *N*-heterocycles **253** by oxidative cyclization/migration tandem reaction with *in situ*-generated hypervalent iodine species. In this process, the Selectfluor could be used as terminal oxidant to oxidize iodoarene or iodoalkane catalyst to produce the crucial I(III) reagents. Notably, this method exhibited good functional group tolerance and the corresponding 3*H*-indoles could be obtained in good to excellent yield (Figure 11.65).

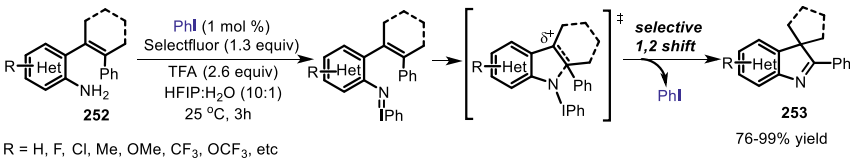
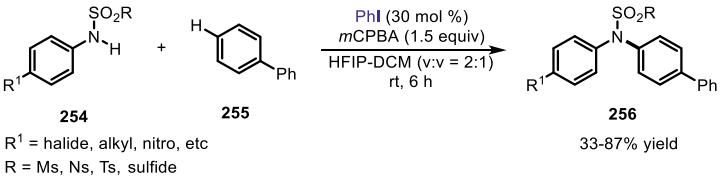


Figure 11.65: Synthesis of 3*H*-indoles via oxidative cyclization/migration mediated by I(III) generated *in situ*.

11.4.3 Intermolecular oxidative coupling

In 2018, Mal and Maiti [107] realized a PhI/*m*CPBA-mediated intermolecular oxidative C–N bond formation reaction between *N*-acylation of sulfonanilides **254** and biphenyls

255, affording a selective synthesis of biacyl sulfonamides **256** via soft–hard acid–base (SHAB) control. The mechanistic pathway first involved the *in situ* formation of hypervalent iodine species from the reaction between PhI and *m*CPBA. Next, the deprotonated nitrenium ions **257** were obtained by the oxidation of substrates **254** by the generated iodine(III) species. Finally, intermediates **257** were eletrophilically attacked by arenes **255** and then deprotonation occurred to produce the desired *N*-arylated sulfonamides **256** (Figure 11.66).



Plausible mechanistic pathway:

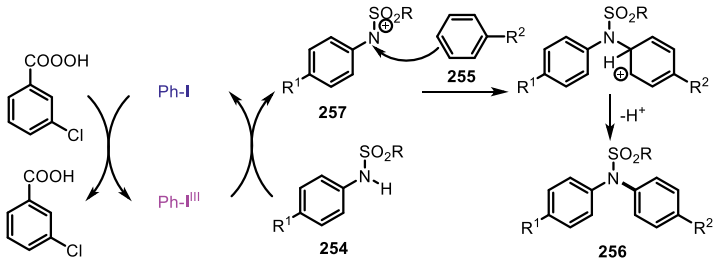


Figure 11.66: Synthesis of biacyl sulfonamides via selective sulfonamidation mediated by I(III) generated *in situ*.

N-aryl amides are one important class of structural motifs found in biologically active molecules. The formation of this class of skeleton via direct oxidative coupling reaction mediated by catalytic amount of organoiodane reagents has also emerged in recent years and many advances have been achieved.

With the *in situ* generated *μ*-oxo hypervalent iodine reagent as an oxidant, the direct oxidative C–N bond formation was realized by Kita's group in 2019 [108]. In this transformation, diverse aryl amides **260** were obtained from a wide range of *N*-methoxyamides **258** and aromatic hydrocarbons **259** (Figure 11.67).

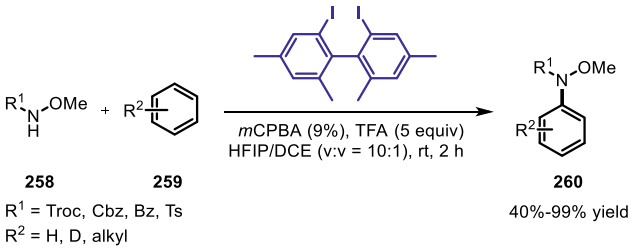
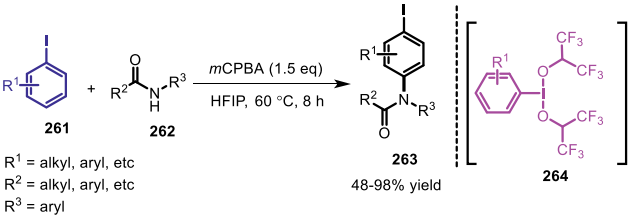


Figure 11.67: Synthesis of aryl amides via oxidative amidation mediated by I(III) generated *in situ*.

In 2021, Li and coworkers [109] discovered an efficient method for the synthesis of different *N*-aryl amides **263** from the reaction of acylanilides **262** and iodobenzenes **261** through an oxidative cross-dehydrogenative coupling under the metal-free conditions. The mechanism of this C–N bond formation involves the oxidation of iodobenzenes **261** to iodosylbenzene, which reacted with HFIP to give the oxidative $PhI(OCH(CF_3)_2)_2$. Next, iodobenzene could be oxidized by this *in situ*-generated $PhI(OCH(CF_3)_2)_2$, via single electron transfer, to give the radical cation **265**, which was transformed into its stable resonance structure **265'**. The nucleophilic addition of substrates **262** to intermediates **265'** could construct the C–N bond to afford radical intermediate **266**, which underwent another single electron oxidation/deprotonation to deliver the target product **263** (Figure 11.68).



Plausible mechanistic pathway:

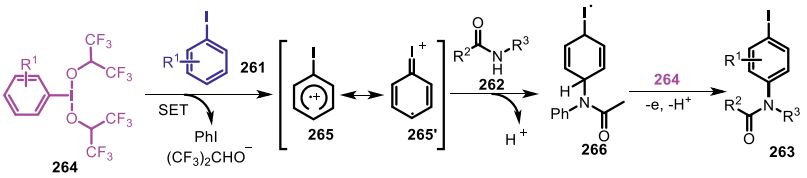


Figure 11.68: Synthesis of *N*-aryl amides via C(sp^2)–N bond formation mediated by I(III) generated *in situ*.

11.4.4 Decarboxylative sulfonamidation

Decarboxylation followed by an C–N bond formation mediated by hypervalent iodine(III) reagents has been realized by Minakata's group [110] in 2014. This novel hypervalent iodine species containing an I–N bond **269** was produced *in situ* from PIDA and $NHTs_2$. In this transformation, β,γ-unsaturated carboxylic acids **267** with various substituents at β-position were converted to the corresponding allylic imides **268** in moderate to good yields (Figure 11.69).

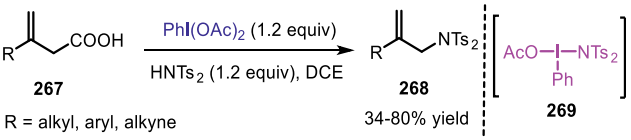
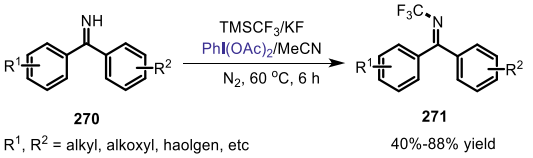


Figure 11.69: Synthesis of allylic imides via decarboxylative sulfonamidation mediated by I(III) generated *in situ*.

11.4.5 Alkylation of imines

Some progress has also been made in developing novel method for the synthesis of N-trifluoromethylated derivatives. In 2015, Wang, Zhu et al. [111] found an electrophilic CF_3-based hypervalent iodine reagent, formed *in situ* from the reaction of PIDA and Ruppert–Prakash reagent in the presence of KF, could be used as trifluoromethylated agent to construct C–N bond. The conversion of N–H ketimines **270** to the corresponding N–CF_3 derivatives **271** was achieved mediated by this $[PhICF_3]^+$ species. Mechanistically, the reaction of substrates **270** and $[PhICF_3]^+$ produced intermediates **272**, which underwent deprotonation followed by reductive elimination of PhI to provide the target products **271** (Figure 11.70).



Plausible mechanistic pathway:

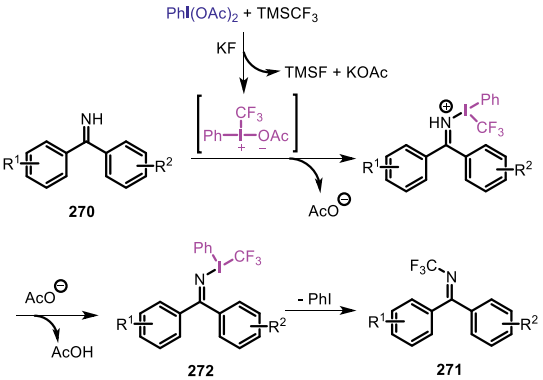
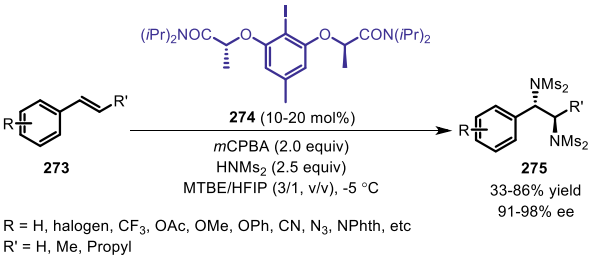


Figure 11.70: Synthesis of *N*-trifluoromethylated compounds via *N*-trifluoromethylation mediated by I(III) generated *in situ*.

11.4.6 Diamination

Vicinal diamines are privileged structural motifs in diverse fields of the biomedicinal and pharmaceutical sciences. The development of novel methods for the synthesis of this structure has therefore received increasing attention. In 2017, Muniz's group [112] realized an enantioselective catalytic vicinal diamination of styrenes **273** induced by *in situ*-formed hypervalent iodine species. Diverse vicinal diamines **275** were obtained in high enantiomeric excess under entirely intermolecular reaction control. It was postulated that the mechanistic pathway first involved the *in situ*-generation of

iodine(III) reagents from the oxidation of chiral iodine **274** by *m*CPBA. Next, the hypervalent iodine reagent would interact with bislactamide motif to induce helical chirality, affording scenario **276**, which was converted to the diastereomerically highly enriched aminoiodinated catalyst state **277**. Then the reductive displacement occurred in **277** to form cyclic intermediates **278**, with the removal of iodoarene. Finally, the cyclic intermediate **278** underwent nucleophilic opening to form desired diamines **275** through the construction of the second C–N bond (Figure 11.71).



Plausible mechanistic pathway:

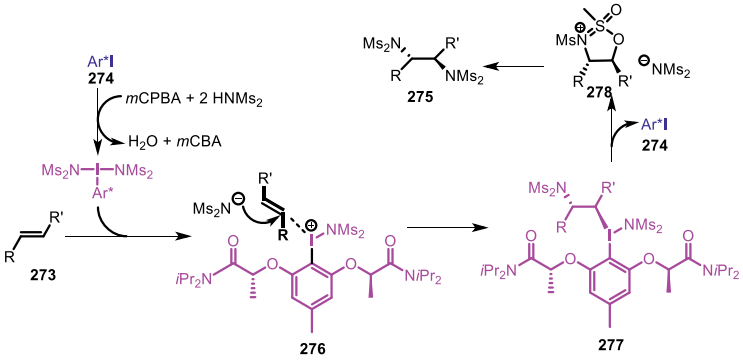
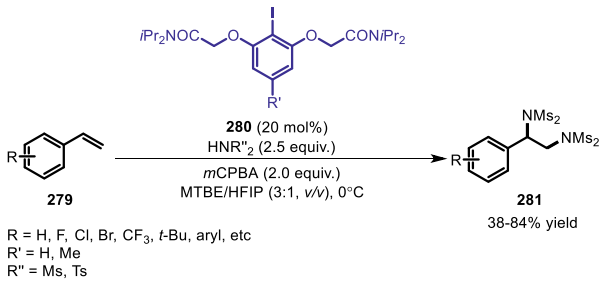


Figure 11.71: Synthesis diamines of via diamination mediated by chiral I(III) generated *in situ*.

In 2019, the same research group [113] also developed a rapid and productive vicinal diamination of styrenes **279** to afford diamines **281** in moderate to good yields by using achiral aryliodine catalyst **280**, which has amide-functionalized side arms. A possible mechanism was proposed for this transformation. First, the reaction of iodoarene with *m*CPBA and bis-sulfonimides generated bisimido iodine(III), which could further react with substrate styrenes **279** to give intermediates **282**. According to their previous work, the desired products **281** were produced from intermediates **282**, with aryliodine catalyst **280** regenerated and entered into the next catalytic cycle (Figure 11.72).



Plausible mechanistic pathway:

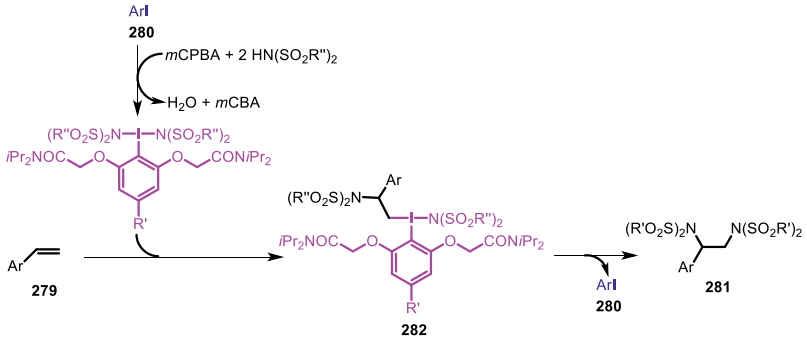
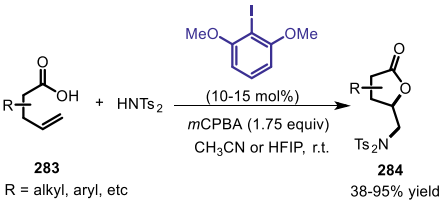


Figure 11.72: Synthesis of diamines via C(sp^2)–N bond formation mediated by I(III) generated *in situ*.

11.4.7 Aminolactonization

In 2021, He and coworkers [114] found that an aryl iodine(III)-mediated oxidative C–O and C–N coupling reaction could occur in unactivated alkenes **283** to give the aminolactonization products **284**. The mechanism was postulated to involve first the formation of aryl-λ^3-iodane (ArI(NTs_2)$_2$) *in situ* through the oxidation of aryl iodine by *m*CPBA in $HNTs_2$. Then aryl-λ^3-iodane (ArI(NTs_2)$_2$) underwent dissociation to deliver the key intermediates $[ArINTs_2]^+$ and $[NTs_2]^-$. Next, through electrophilic addition with $[ArINTs_2]^+$, substrates **283** could give iodonium intermediates **285**. Subsequently, iodonium intermediates **285** underwent intramolecular nucleophilic cyclization to deliver intermediates **286**, which removed $[NTs_2]^-$ and further underwent nucleophilic addition to yield products **284**, along with the regeneration of aryl iodine (Figure 11.73).

In 2021, the same group [115] reported that the same iodoarene also could promote the oxyamination of unactivated alkenes **288**. Aryl iodine **289** could first be oxidized by *m*CPBA with $HNTs_2$ to form hypervalent iodine agents *in situ*. Various 5-imino-2-tetrahydrofuranyl methanamine derivatives **290** could be obtained in generally good to excellent yields by this aryl iodine-mediated catalytic approach (Figure 11.74).



Plausible mechanistic pathway:

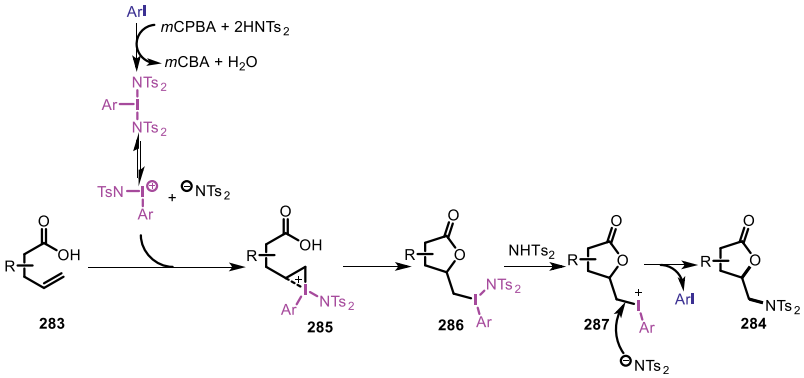


Figure 11.73: Synthesis of amino lactones via aminolactonization mediated by I(III) generated *in situ*.

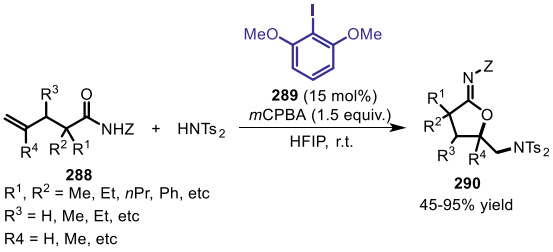


Figure 11.74: Synthesis of 5-imino-2-tetrahydrofuranyl methanamines via oxyamination mediated by I(III) generated *in situ*.

11.5 Formation of carbon–halogen bonds

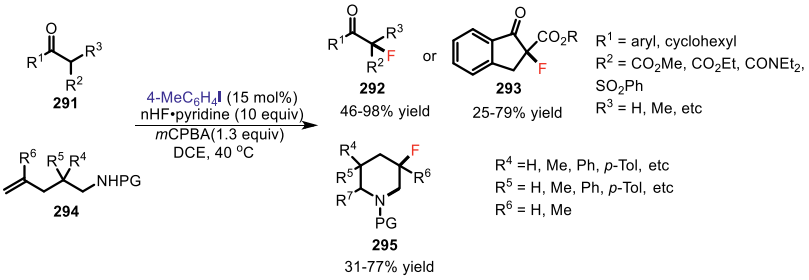
The construction of carbon–halogen bonds mediated by *in situ*-generated hypervalent iodine reagents has attracted great attention and has been intensively studied during the past decades.

11.5.1 Formation of C–F bonds

Enantioselective incorporation of fluoro atom into organic molecules is highly valuable in modern drug discovery and agrochemical development. (Difluoroiodo)arenes

($ArIF_2$), a useful fluorinating reagent, could be formed *in situ* from the corresponding iodoarene.

In 2014, Shibata's group [116] established an efficient iodoarene-induced method for constructing C–F bond via fluorination. In this reaction, through nucleophilic fluorination of β-dicarbonyl compounds **291**, α-fluorinated β-ketoesters, β-ketosulfones, and β-ketoamides **292** with a tertiary or quaternary fluorinated stereogenic center were obtained in good to high yields. Interestingly, when *ω*-amino-alkenes **294** were subjected into the same reaction conditions, they would undergo intramolecular aminofluorination to afford diverse cyclic amines with a tertiary or quaternary fluorinated stereogenic center. For the plausible mechanism, the hypervalent iodine compound, i.e., $ArIF_2$ was generated *in situ* from the system of catalytic amount of iodoarene, *m*CPBA, and hydrogen fluoride. The resulting $ArIF_2$ would activate enolized β-dicarbonyl compounds **291** and then be nucleophilically attacked by fluoride anion



Plausible mechanistic pathway:

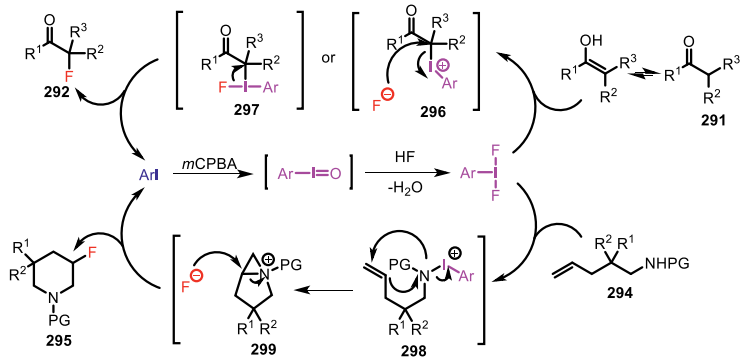


Figure 11.75: Synthesis of α-fluorinated β-dicarbonyl compounds and fluorinated cyclic amines via fluorination mediated by I(III) generated *in situ*.

to give title products **292**. It was also postulated that the ligand coupling pathway via intermediates **297** might be another possibility. In this intramolecular aminofluorination process, the nitrogen of aminoalkenes **294** would be oxidized by $ArIF_2$ to give intermediates **298**, which could be converted to aziridinium intermediates **299**

through the nucleophilic attack from the olefin moiety onto the electron-deficient nitrogen center. Finally, the nucleophilic fluorination of intermediates **299** would occur to provide target products **295** (Figure 11.75).

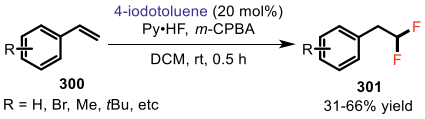
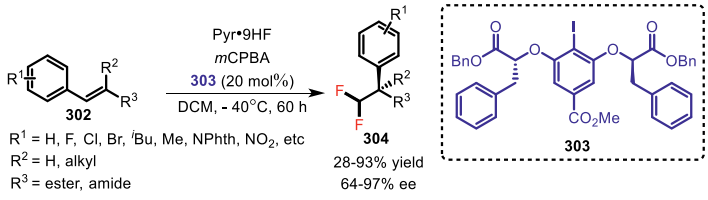


Figure 11.76: Synthesis of (2,2-difluoroethyl) arenes via fluorination mediated by I(III) generated *in situ*.

In 2015, Kitamura's group [117] discovered an alternative approach for the synthesis of diverse (2,2-difluoroethyl)arenes **301** from styrenes **300** through fluorination catalyzed by hypervalent iodine(III) agents. When using 4-iodotoluene as a catalyst and *m*CPBA as a terminal oxidant in the presence of pyridine·HF complex, the hypervalent iodine(III) species was generated *in situ*. Notably, this transformation involved an 1,2-aryl migration to introduce a 2,2-difluoroethyl group into arenes (Figure 11.76).

Over the past decade, the difluoromethyl group (CF_2H) has attracted much attention from organic and medicinal chemists, because it's slightly acidic C–H bond and could also be used as a lipophilic hydrogen-bond donor. In 2016, Jacobsen's group [118] achieved the construction of versatile chiral building blocks containing difluoromethyl groups from β-substituted styrenes **302** through a hypervalent iodine(III)-mediated asymmetric, migratory geminal difluorination. The hypervalent iodine(III) agents were proposed to be generated *in situ* from the corresponding chiral aryl iodine and *m*CPBA in the presence of hydrogen fluoride pyridine. The substrates were then activated by iodine(III) species to give intermediates **305**, which then were converted to the



Plausible mechanistic pathway:

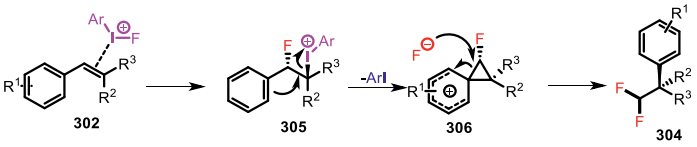
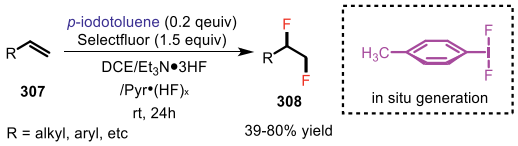


Figure 11.77: Synthesis of chiral building blocks bearing difluoromethyl groups via difluorination mediated by I(III) generated *in situ*.

phenonium ion intermediates **306** through rearrangement, along with the regeneration of precatalyst. Phenonium ion intermediates **306** were subsequently attacked by fluoride anion to yield title products **304** (Figure 11.77). In 2018, Houk, Xue and coworkers [119] further explored mechanism and origins of chemo- and stereoselectivities of difluorinations of β-substituted styrenes **302** mediated by C_2-symmetric chiral aryl iodides through computational model.



Plausible mechanistic pathway:

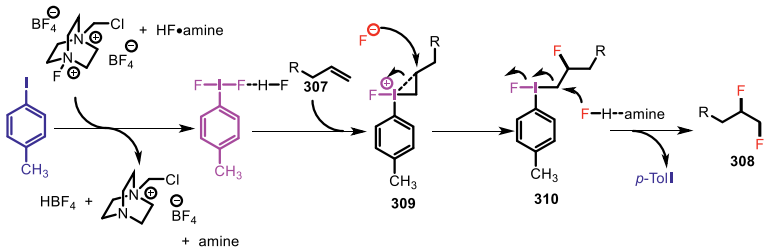
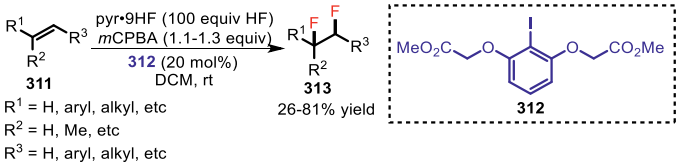


Figure 11.78: Synthesis of vicinal difluoride analogs via vicinal difluorination mediated by I(III) generated *in situ*.

In 2016, Gilmour and coworkers [120] discovered a simple method for the catalytic vicinal difluorination of simple olefins **307** through double C–F bond construction with inexpensive *p*-iodotoluene as the catalyst. A variety of olefins were found to be suitable for this vicinal difluorination. According to mechanistic pathway, oxidation of iodoarene first generated the active *p*-TolIF$_2$, which subsequently reacted with terminal olefins to give transient cations **309**. After displacement sequence by fluorides, intermediates **309** were converted products **308** (Figure 11.78).

In the same year, Jacobsen's group [121] reported the synthesis of vicinal difluoride products **313**, which possessed an interesting characteristic of adopting preferred gauche conformations. One of the key steps in their route was a diastereoselective alkene 1,2-difluorination using the *in situ*-generated hypervalent iodine(III) reagent. The alkenes **311** with all types of substitution patterns were treated with ArIF$_2$ in DCM at room temperature to give the corresponding vicinal difluoride products **313** in lower to good yields with high diastereoselectivities. A possible mechanism for the 1,2-difluorination of alkenes was proposed. Frist, the reactive hypervalent iodine(III) reagents was produced *in situ* from aryl iodine catalyst, *m*CPBA and py·HF via stepwise oxidation and subsequent deoxyfluorination. Then, alkenes **311** would react with ArIF$_2$



Plausible mechanistic pathway:

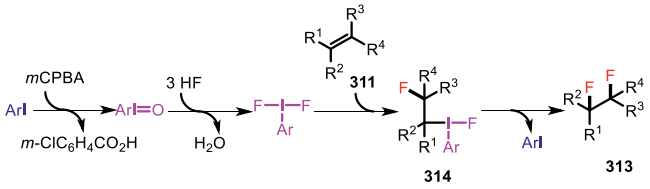


Figure 11.79: Synthesis of vicinal difluoride via 1,2-difluorination mediated by chiral I(III) generated *in situ*.

to give intermediates **314**, which then finally were converted to the corresponding products **313** through ligand coupling along with the regeneration of precatalyst **312** (Figure 11.79).

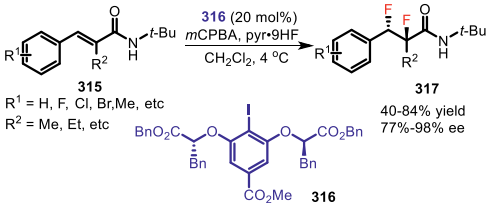


Figure 11.80: Synthesis of vicinal difluoride via 1,2-difluorination mediated by chiral I(III) generated *in situ*.

In 2019, Jacobsen and coworkers [122] continued to disclose that the chiral hypervalent iodine, which derived from the catalytic chiral aryl iodide **316** plus *m*CPBA and HF-pyridine, could promote the diastereoselective 1,2-difluorination of *tert*-butyl cinnamamides **315**. According to the results, the *tert*-butyl group of substrates was found to have a great influence on the enantioselectivity of 1,2-difluorination and the corresponding products **317** could be converted into 1,2-difluoride-containing primary amides through the cleavage of the *tert*-butyl group (Figure 11.80).

In 2016, the same group [123] reported a route to access 4-fluoroisochromanones **320** in moderate yields under metal free conditions, utilizing chiral aryl iodine-promoted enantioselective fluorolactonization of styrene derivatives **318** with HF-pyridine used as a source of nucleophilic fluoride. In this transformation, the *in situ* formed hypervalent iodine(III) species would react with substrates **318** to give key intermediates **321**, which then gave the corresponding lactones containing fluorine-bearing stereogenic centers in high enantio- and diastereoselectivity (Figure 11.81).

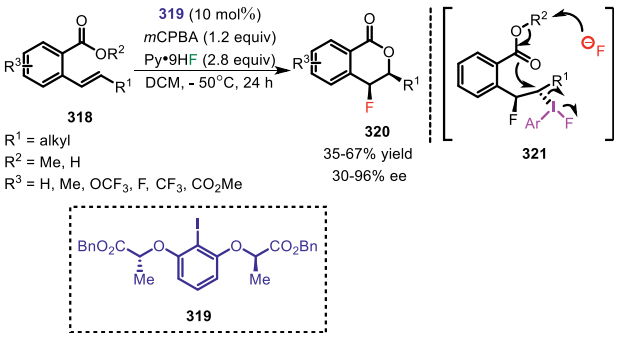


Figure 11.81: Synthesis of 4-fluoroisochromanones via fluorolactonization mediated by chiral I(III) generated *in situ*.

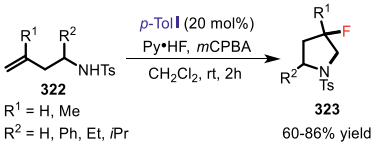
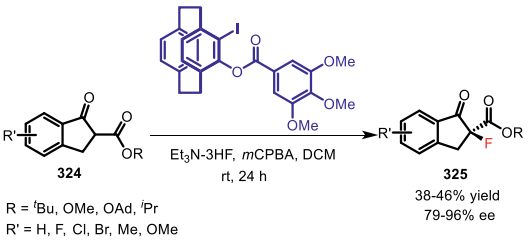


Figure 11.82: Synthesis of *N*-tosyl-3-fluoropyrrolidines via difluorination mediated by I(III) generated *in situ*.

In 2017, Oyamada's group [124] achieved the synthesis of *N*-tosyl-3-fluoropyrrolidines **323** from homoallylamine derivatives **322** through intramolecular aminofluorination, enabled by the hypervalent iodine(III) species generated from the *p*-iodotoluene/*m*CPBA/Py·HF regent system (Figure 11.82).

In 2018, Zheng's group [125] reported a highly enantioselective oxidative fluorination of β-ketoesters **324**, mediated by the *in situ*-generated chiral hypervalent iodine species from planar chiral iodoarenes based on [2.2] paracyclophane and *m*CPBA in the presence of 3HF–Et_3N. It is worth mentioning that *m*CPBA was used as a terminal oxidant and 3HF–Et_3N acted as a nucleophilic fluoride source. They proposed that the oxidation of ketone of substrates β-ketoester **324** by hypervalent iodine compounds gave O-bonded hypervalent iodine species **326**, which underwent 1,3-migration to form intermediates **327**. Reductive elimination of intermediates **327** occurred to give the desired product **325** and regenerated the catalyst (Figure 11.83).

Recently, α-fluorocarbonyl motif has become a prominent target scaffold. In 2020, accessing to α-fluoroketones **329** from terminal and internal alkynes **328** catalyzed by organoiodine was reported by Gilmour and coworkers [126]. Using *p*-TolI and Selectfluor in an amine/HF complex, the active *p*-$TolIF_2$ could be generated *in situ*. According to the results, the oxygen of the aryl ketone came from water (Figure 11.84).



Plausible mechanistic pathway

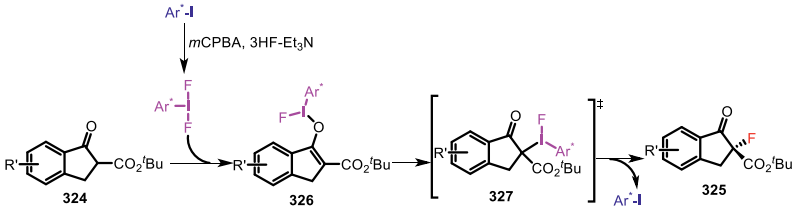


Figure 11.83: Synthesis of fluorinated compounds via symmetric nucleophilic α-fluorination mediated by chiral I(III) generated *in situ*.

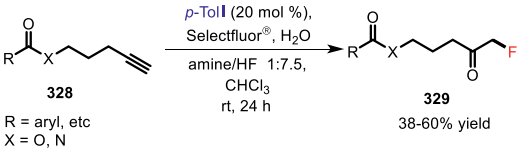


Figure 11.84: Synthesis of α-fluoroketones via fluorohydration mediated by I(III) generated *in situ*.

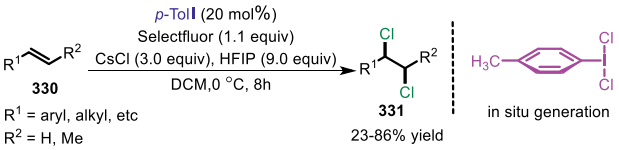


Figure 11.85: Synthesis of 1,2-dichloro compounds via vicinal dichlorination mediated by I(III) generated *in situ*.

11.5.2 Formation of C–Cl bonds

In 2019, Gilmour's group [127] disclosed an *in situ*-generated *p*-TolICl$_2$-mediated vicinal dichlorination of inactivated alkenes **330**. The active *p*-TolICl$_2$ was derived from the reaction of *p*-TolI and Selectfluor in the presence of CsCl. This method furnished a series of dichloride compounds **331** in yields up to 86%. It was worth noting that 1,2-dichloro moiety in an array of bioactive natural products of both terrestrial and marine origin also could be constructed by the method (Figure 11.85).

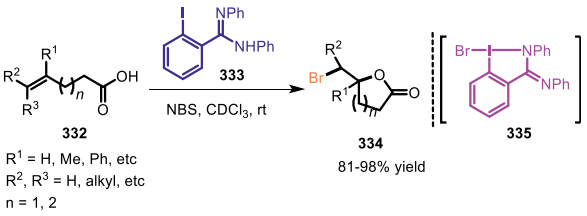


Figure 11.86: Synthesis of bromolactones via bromination mediated by I(III) generated *in situ*.

11.5.3 Formation of C–Br bonds

The hypervalent iodine–bromine reagent **335** is an efficient electrophilic bromine source. In 2006, Braddock's group [128] discovered that the *ortho*-substituted iodobenze **333** could react with *N*-bromosuccinimide (NBS) to form bromoiodinanes(III) species **335** *in situ*, which then transfer the electrophilic bromine to the substrate alkenes **332**, leading to the formation of bromolactone products **334** (Figure 11.86).

In 2012, Gulder and coworkers [129] reported a hypervalent iodine(III)-catalyzed bromocarbocyclization reaction for the synthesis of C-3-disubstituted oxoindoles **338**

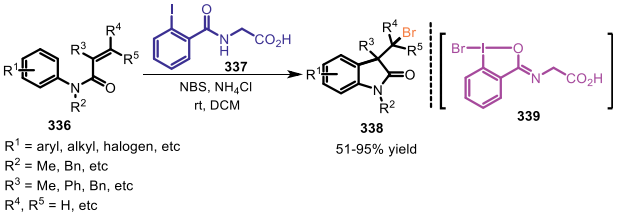


Figure 11.87: Synthesis of C-3-disubstituted oxoindoles via bromocarbocyclization mediated by I(III) generated *in situ*.

from the substrates **336** bearing electron-poor double bonds. Here the active iodine(III) reagent **339**, an electrophilic bromination agent, was generated *in situ* from the reaction of iodobenzamide **337** and oxone. This strategy displayed a complete selectivity of forming five-membered ring. A variety of substrates involving ketones or silyl ethers

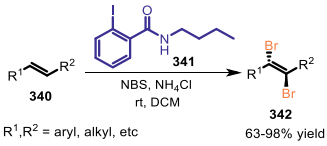


Figure 11.88: Synthesis of dibrominated compounds via dibromination mediated by I(III) generated *in situ*.

were applicable by this method. Especially, the brominated products **338** could be further transformed into structurally complex compounds, such as physostigmine (Figure 11.87).

In 2014, the same group [130] disclosed that by changing the substitutes of iodobenzamide catalyst, alkenes **340** could be converted to the dibrominated products **342**

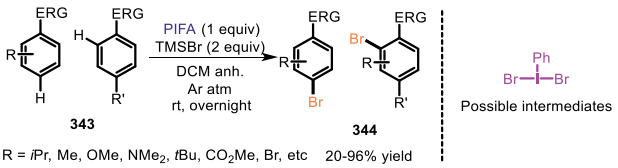


Figure 11.89: Synthesis of brominated compounds via bromination mediated by I(III) generated *in situ*.

in excellent yields. It was found that dibromination could also be achieved by the hypervalent iodine–halogen reagents generated *in situ* (Figure 11.88).

In 2020, Vallribera, Cossio et al. [131] developed a metal-free bromination of arenes **343** to access *para*-brominated compounds **344** via selective C–Br bond formation. This method was realized by using the combination of PIFA and TMSBr and was applicable to a broad range of substrates. According to the results, the *in situ* generated $PhIBr_2$ was proposed an active intermediate. Unfortunately, the mixing PIFA and TMSBr could not separate $PhIBr_2$ due to the unstable I–Br bonds (Figure 11.89).

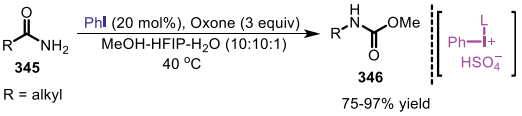


Figure 11.90: Synthesis of carbamates via Hofmann rearrangement mediated by I(III) generated *in situ*.

11.6 Rearrangement reaction

Hypervalent iodine species formed *in situ* from the aryl iodine have also found application in rearrangement reactions.

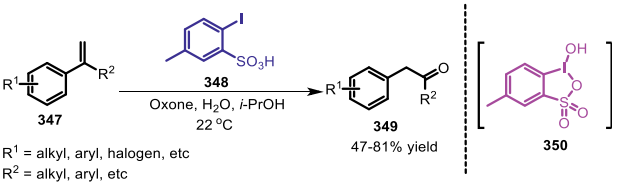


Figure 11.91: Synthesis of ketones via oxidative rearrangement mediated by I(III) generated *in situ*.

In 2010, Zhdankin, Yoshimura and coworkers [132] realized an efficient organoiodine-catalyzed Hoffmann rearrangement of carboxamides **345**, leading to the formation of carbamate compounds **346**. In this conversion, organoiodine reacted with oxone in the presence of HFIP to afford the hypervalent iodine reagent *in situ* (Figure 11.90).

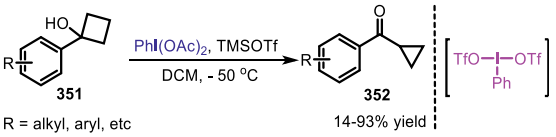


Figure 11.92: Synthesis of aryl cyclopropyl ketones via ring contraction mediated by I(III) generated *in situ*.

In 2013, Purohit and coworkers [133] discovered that 1,1′-disubstituted olefins **347** could undergo [1,2]-aryl migration by reacting with the *in situ*-generated hypervalent iodine species **350** to form homobenzylic ketones **349**. In the presence of oxone, 4-Me-IBS **348** were *in situ* converted to the active hypervalent iodine reagents **350** (Figure 11.91).

In 2018, Peng and coworkers [134] reported that treating cyclobutanols **351** with $PhI(OAc)_2$ in the presence of TMSOTf, an oxidative ring contraction could occur to afford aryl cyclopropyl ketones **352**. The oxidant of this reaction was $PhI(OTf)_2$, which formed *in situ* from $PhI(OAc)_2$ and TMSOTf (Figure 11.92).

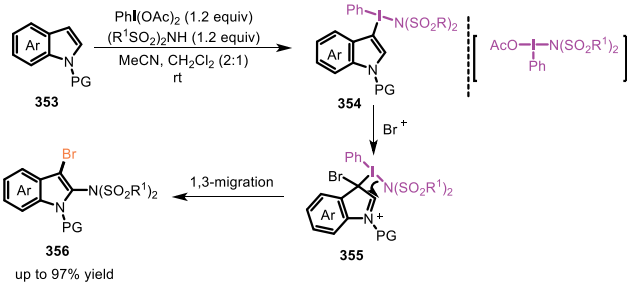


Figure 11.93: Synthesis of 2-bis(sulfonyl)amino-3-bromoindole via 1,3-migration mediated by I(III) generated *in situ*.

In 2015, Togo, Moriyama et al. [135] reported an alternative approach to synthesize 2-bis(sulfonyl)amino-3-bromoindoles **356** from indole compounds **353** via $C_{sp}{}^2$–H dual functionalization. In this reaction, various indoles and imides were first converted to indolyl(phenyl)iodonium(III) imides **354** mediated by amide-combined hypervalent iodine (III) species. The active intermediates **354**, as an amino reagent, dummy protection and reaction activator, was then transformed into the target products **356** through bromination followed by 1,3-migration. It is worth noting that PIDA could react

with bis(tosyl)imide to produce the novel amide-combined hypervalent iodine reagents *in situ* (Figure 11.93).

11.7 Conclusions

From the above various synthetic transformations, it is obvious the oxidative hypervalent iodine species could be generated *in situ* from the corresponding aryl iodine and terminal oxidants, thus avoiding the use of stoichiometric hypervalent iodine oxidant and minimizing the accumulation of unwanted waste. The goal of writing this review is to expose the recent development of applying the *in situ*-generated hypervalent iodine species in organic synthesis, providing references and highlights for further developing innovative and creative synthetic methods. From economic and environment viewpoints, the recycling and catalytic utilization of hypervalent iodine agents deserves further development. In this regard, more and more efficient organic transformations, especially the asymmetric reactions, mediated by *in situ*-generated hypervalent iodine species are expected to be reported in the future.

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12 Zwitterionic imidazolium salt: an effective green organocatalyst in synthetic chemistry

Abstract: An environmentally benign, stable yet efficient organocatalyst is highly desirable from the viewpoint of green chemistry and catalysis. Imidazole-based zwitterionic-type molten salts are a new type of organocatalysts with high catalytic application in various organic transformations with added advantage of room temperature ionic liquid (RTIL) property. Most importantly, these ionic-liquid catalysts are easily recyclable and subsequently reusable for multiple times without loss of significant catalytic efficiency. It has also been evident that C2–H of the imidazole has a vital role in catalyzing the reaction *via* electrophilic activation. Moreover, by changing the cations and/or anions, the properties of ILs can be tuned in many ways. In this article, the role of imidazolium zwitterionic molten salts as an organocatalyst for selective organic transformations including *syn*-selective aza-Henry reaction, Erlenmeyer reaction, synthesis of different heterocycles and their functionalization and regioselective ring-opening reactions has been elaborated chronically which will definitely be helping to the readers to explore this new class of organocatalyst for further applications.

Keywords: green synthesis; organocatalyst; task specific ionic liquid; zwitterionic imidazolium salt.

12.1 Introduction

Organocatalysis, a new field of catalysis in organic synthesis, has increased its interest enormously in the preceding few years as a consequence of both the novelty of the concept and environment-friendly utilities in synthesis and hence steps toward sustainable green chemistry [1]. More prominently, the efficiency as well as selectivity of various organocatalytic reactions fulfills the standards of conventional organic reactions [2]. Therefore, organocatalytic reactions are becoming powerful tools in the construction of a variety of bioactive molecules, fine chemicals, and precursors of several biologically active molecules [3]. The effective use of organocatalysts under

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solvent-free conditions and at room temperature is of great importance as it eradicates the unwanted volatile organic compounds and boosts the greenness in the process [4].

In this scenario, recent years have witnessed significant developments on imidazole-based zwitterionic-type molten salts catalysis in organic synthetic chemistry [5]. They have been realized as catalyst precursors, catalysts, reagents, and potential solvents for several organic conversions and provide ecofriendly protocols. Moreover, the application ILs/ILs-based molten salts as energy storage materials, such as battery applications due to their nonflammable and high conduction properties is very significant in the present state of energy crisis [6]. Besides, the key advantages of these room temperature stable zwitterionic-type molten salts ionic-liquid catalysts are easily recyclable and subsequent reusable for multiple times without loss of significant catalytic efficiency. Numerous ionic liquids containing functional groups like amine, amide, ether, alcohol, acid, urea, and thiourea into the side chain of imidazolium cation are already renowned [7]. Moreover, by changing the cations and/or anions, the properties of ILs can also be tuned in many ways [8]. In general, reactions of the various imidazoles with 1,4-butane sultone yield the targeted zwitterionic-type molten salts [9]. The synthetic strategy of zwitterionic imidazolium molten salt is represented in Figure 12.1.

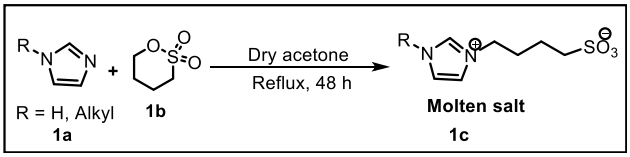

Figure 12.1: Synthetic strategy of zwitterionic type molten salt.

Our group extensively worked on imidazolium zwitterion catalyzed organic transformations since the last few decades. In this article, we will systematically disclose the role of imidazole-based zwitterionic-type molten salts (Figure 12.2) as an organocatalyst for some chemical transformations such as *syn*-selective aza-Henry reaction, Erlenmeyer reaction, synthesis of different heterocycles and their functionalization, regioselective ring-opening reactions and so on based on our reports as well as reports by other groups.

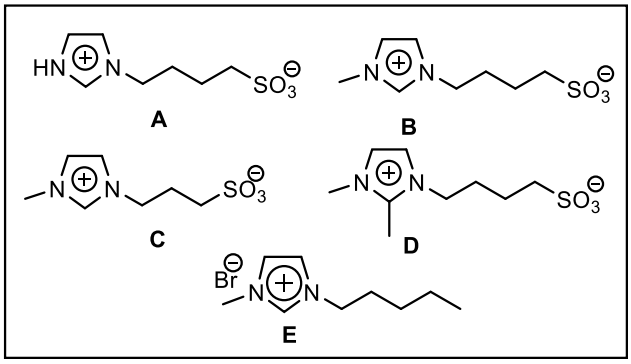

Figure 12.2: Some examples of zwitterionic type molten salt.

12.2 Zwitterionic type molten salt-catalyzed *syn*-selective aza-Henry reaction

Aza-Henry reaction is one among few very popular fundamental carbon–carbon bond-making reactions in organic chemistry [10]. Aza-Henry (nitro-Mannich) reaction permits synthesis of β-nitroamines which have two vicinal stereogenic centers containing nitro and amino functional groups. The obtained nitroalkenes were found in many synthetically useful compounds and further giving access to different transformations by converting the nitro group to other interesting functional groups like amine, hydroxyl amines, and oxime or nitrile [11]. Because of the extensive utility of β-nitroamine compounds, various groups have been reported synthesis of these compounds *via* reaction between imines and nitroalkanes in the presence of either metal catalysts or organocatalysts. Majority of them have reported the *anti* isomer as major product with only few reports available which have reported aza-Henry reaction for the production of *syn*-isomer. In this regard, our group [12] first reported a direct method by one-pot reaction of various amines, aldehydes and nitroalkanes at ambient temperature under solvent-free conditions by the use of zwitterionic type molten salts (Figure 12.3). We obtained the *syn*-isomer **2d** as the main product with very good diastereoselectivity and excellent yields. The reaction was catalyzed by both zwitterionic salts 4-(1-imidazolium)butanesulfonate **A** or 4-(3-methylimidazolium)butanesulfonate **B** (Figure 12.2), however, **A** showed better selectivity than that of **B.** This three-component condensation methodology was applicable for a wide range of substrates to generate a library of *syn*-β-nitroamines with up to 92% yield. Interestingly, aliphatic aldehydes and amines took part in the reaction in slower rate and afforded a mixture of products. A suitable mechanism was proposed for this reaction as shown in Figure 12.3. Firstly, generation of imine (**2i**) was assisted by electrophilic activation of the carbonyl group *via* H-bonding with C2–H atom of imidazolium moiety. Then, nitroalkane (**2c**) reacted with imine (**2i**) to produce the β-nitroamine (**2d**) as the final product.

12.3 Synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthol

Amidoalkyl and carbamatoalkyl naphthols are vital intermediates for the formation of 1,3-amino oxygenated products. Molecules having 1,3-amino oxygenated functional groups are found in a wide range of bioactive compounds, for example, nucleoside antibiotics and HIV protease inhibitors [13]. Because of variety of applications, recent research interest has focused on the generation of 2-amidoalkyl and 2-carbamatoalkyl naphthol. In this scenario, our group reported [14] a new reaction strategy between 2-naphthol, aldehyde, and carbamate or amide to obtain a series of 2-amidoalkyl and

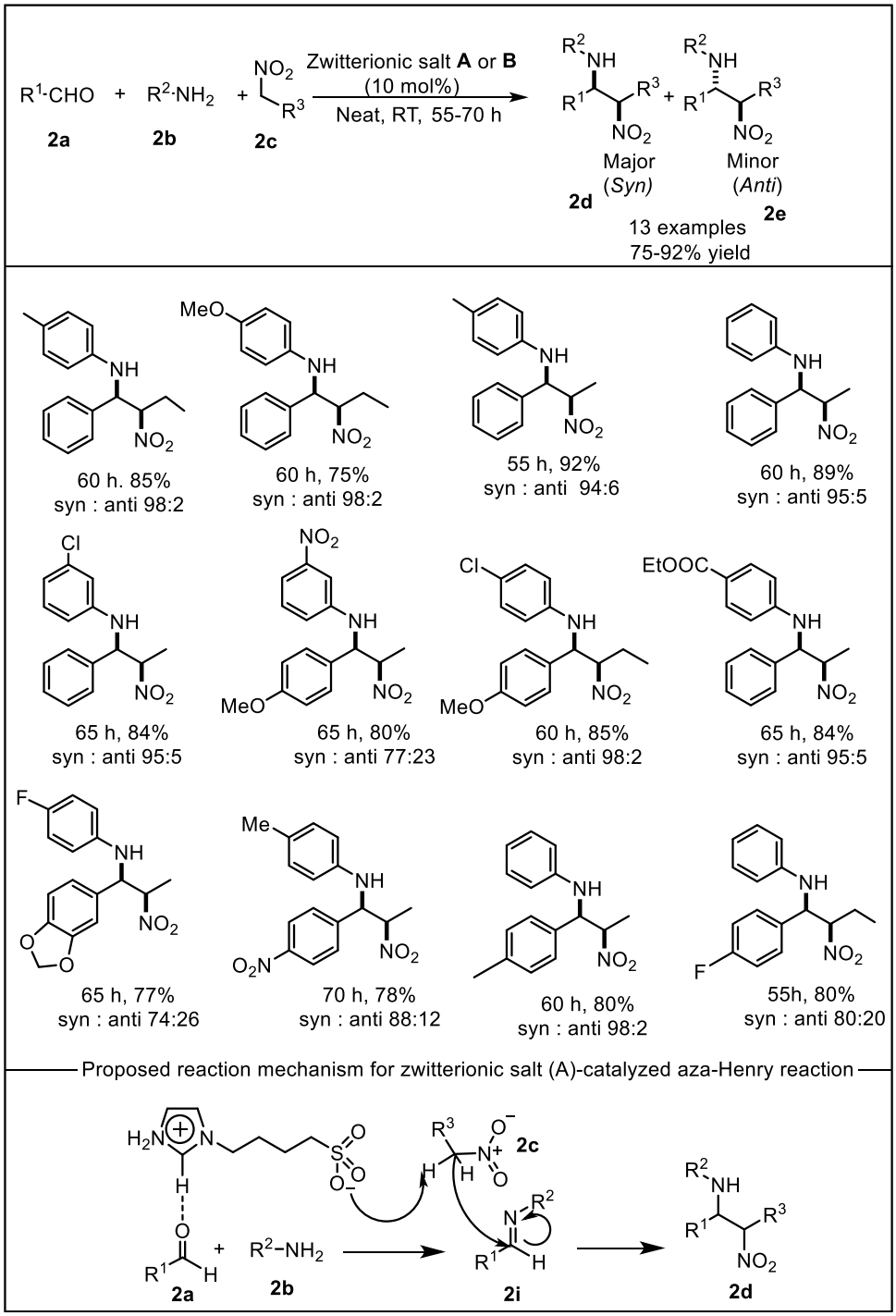

Figure 12.3: Zwitterionic molten salt-catalyzed *syn* selective aza-Henry reaction (Hajra method).

2-carbamatoalkyl naphthol derivatives (**3d**) using zwitterionic-type molten salt **A** under solvent-free conditions (Figure 12.4). A variety of substituted aldehydes as well as carbamates or amides were tested in combination with 2-naphthol and the condensation products were achieved in good to excellent yields (72–90%). It is worthy to mention here that present methodology worked well for both aliphatic and aromatic aldehydes. Important advantages were broad substrate scope, short reaction time, high yields formation and large-scale applicability. The most possible mechanism for this reaction was depicted in Figure 12.4. Initially, 2-naphthol **3a** reacted with an aromatic aldehyde **3b** to produce *o*-quinone methide (*o*-QM) intermediate **3i**. After that, nucleophilic conjugate addition of amide or carbamate **3c** on *o*-QM **3i** resulted in formation of amidoalkyl naphthol or carbamato naphthol (**3c**) as the product. Zwitterionic-type molten salt **A** acted as a bifunctional organocatalyst. It might activate both aldehydic carbonyl oxygen and acidic hydrogen of 2-naphthol.

12.4 Synthesis of 3-aminoalkylated indoles

Indole derivatives are also well known and largely found in various synthetic and natural products. Due to variation in structure and biological activities of indole derivatives, functionalization of indole moiety received great research interest to the scientific community. Among various positions, 3-substituted indoles are more common and found in a variety of indole derivatives as well as many natural products. In this context, our research group [15] have reported a simple and effective approach towards the generation of 3-aminolkylated indole derivatives (**4d**) *via* a solvent-free one-pot three-component combination of aldehydes, secondary amins, and indoles using zwitterionic molten salt **A** at 60 °C (Figure 12.5). To our pleasure, catalyst **A** was reused as minimum as six times without significant decrease in catalytic activity. We have checked condensation reaction between varieties of indoles, substituted aldehydes and amines as well and found that the corresponding 3-aminoalkylated indole derivatives were obtained in very good yields (81–88%). Notably, aliphatic aldehydes such as *iso* butyraldehyde and cyclohexanecarboxaldehyde were well tolerated under present reaction conditions and the corresponding products were obtained in very good yields (83–84%). A possible mechanism is represented in Figure 12.5. Firstly, iminium ion **4i** was generated by the assistance of electrophilic activation of the aldehyde carbonyl by H-bonding with the C2–H atom of the imidazolium framework. Then, the nucleophilic attack by indole **4a** to iminium ion **4i** gave the final product i.e., 3-aminoalkylated indole (**4d**).

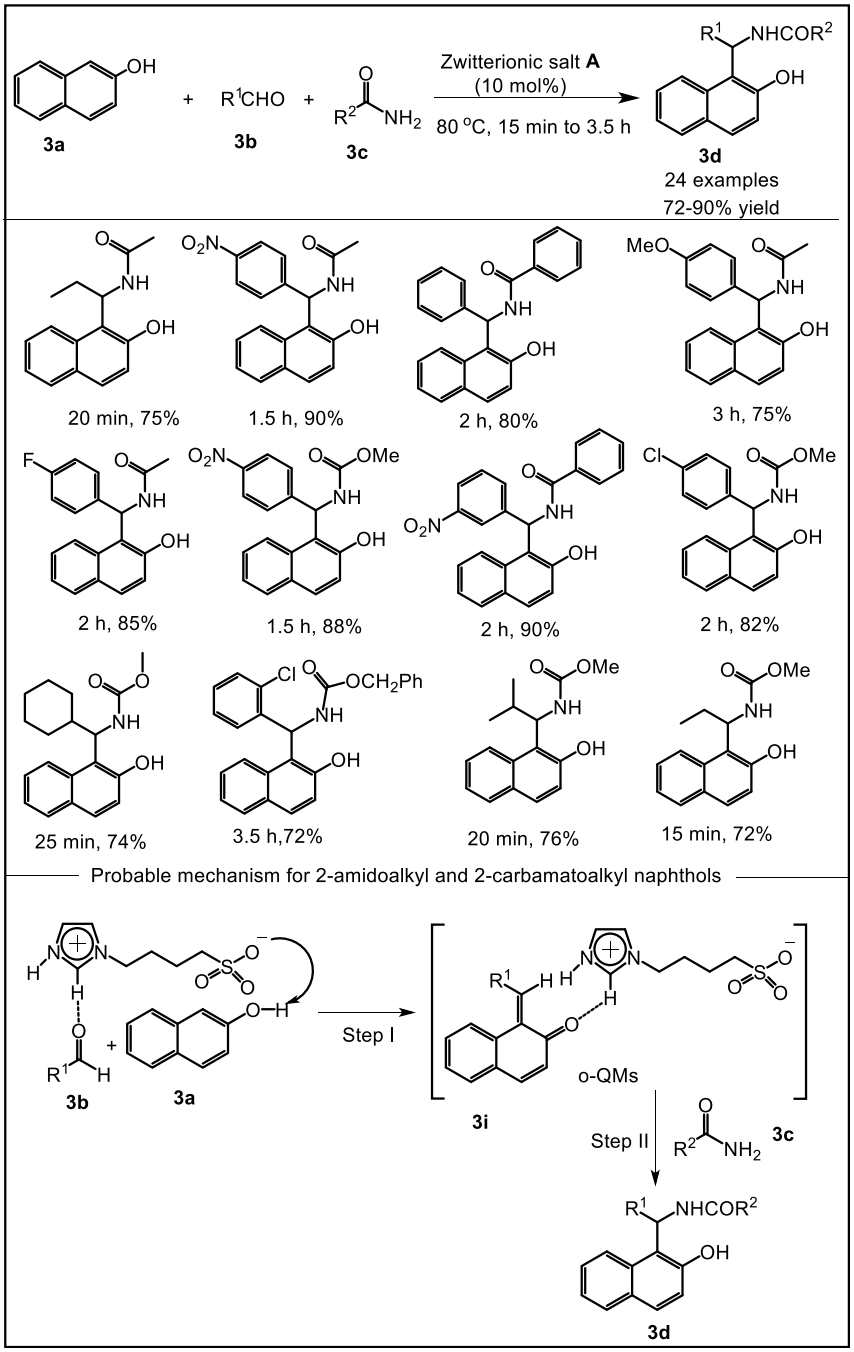

Figure 12.4: Synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthol (Hajra method).

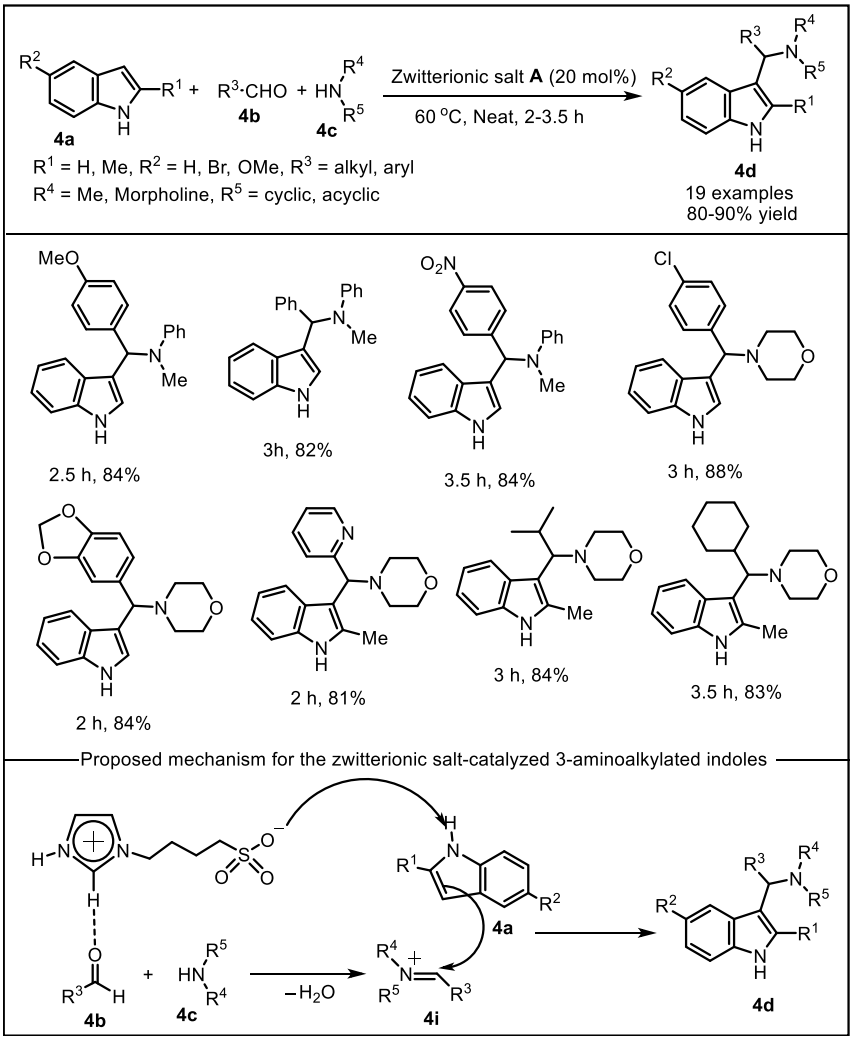

Figure 12.5: Synthesis of 3-aminoalkylated indoles (Hajra method).

12.5 Zwitterionic type molten salt-catalyzed synthesis of multiple substituted imidazoles

The five-membered heterocyclic imidazole rings are a vital structural unit in organic chemistry and largely observed in countless pharmaceutically and biologically interested compounds. As a result, serious efforts have been paid to develop new strategies for synthesis of highly substituted imidazole derivatives without polluting the environment. Considering this background, our group [16] developed an easy and

proficient imidazole-based zwitterionic-type molten salt (**A**) catalyzed methodology for synthesis of a series of 2,4,5-trisubstituted imidazole derivatives **5d** up to 85% yield. The reported three-component condensation strategy used 1,2-dicarbonyl compounds, ammonium acetate or amine, and aldehydes as reactants under solvent-free conditions at 80 °C for 4–7 h. Most interestingly, fruitful results were achieved when amine was mixed with the reaction conditions and obtained 1,2,4,5-tetrasubstituted imidazoles **5e** with up to 82% yields within 5–8 h (Figure 12.6). It was suggested that the catalyst acted as an activator of carbonyl oxygen of aldehyde or 1,2-dicarbonyl compound through H-bond formation with the N–H of the imidazolium moiety.

12.6 Zwitterionic type imidazolium molten salt-catalyzed synthesis of 5-substituted 1*H*-tetrazoles

Tetrazole, a four *N*-atoms containing heterocycle has attracted considerable interest in recent time due to their extensive range of applications in medicinal chemistry [17]. Our group also contributed significantly on synthesis of substituted 1*H*-tetrazoles. According to this method, 1 equiv. of aryl nitriles reacted with 1.5 equiv. of azides in presence of 10 mol% imidazole-based zwitterionic-type molten salt **B** for 10 h at 120 °C [18]. Like the other mentioned methods, this method also did not use any solvent. The desired 5-substituted 1*H*-tetrazoles **6c** were achieved up to 84% (Figure 12.7). Other imidazole-based zwitterionic-type molten salts were tested and observed less efficiency than that of **B**. The authors then tried to find out the effect of C2–H of the imidazole by using 4-(2,3-dimethylimidazolium)butanesulfonate (**D**) as catalyst in the same reaction and found no formation of the desired product. The result confirmed that the C2–H of imidazole part played an important responsibility on the cycloaddition reaction. A broad range of substituted aromatic nitriles irrespective of electron-withdrawing and electron-releasing group responded the reaction under optimized reaction conditions. Moreover, heteroaryl nitrile took part in the reaction and afforded the corresponding product with very good yield. Based on earlier reports, the most probable reaction mechanism was proposed as shown in Figure 12.7. At first, the aryl nitrile was activated by H-bonding with C2–H of **A**. Next, the azide attacked on the C-center of the nitrile to generate the intermediate **6i**. Then, another intermediate **6ii** was formed through a five-membered intramolecular cycloaddition reaction of **6i**. Finally, the desired product **6c** was achieved on releasing a proton from **6ii**.

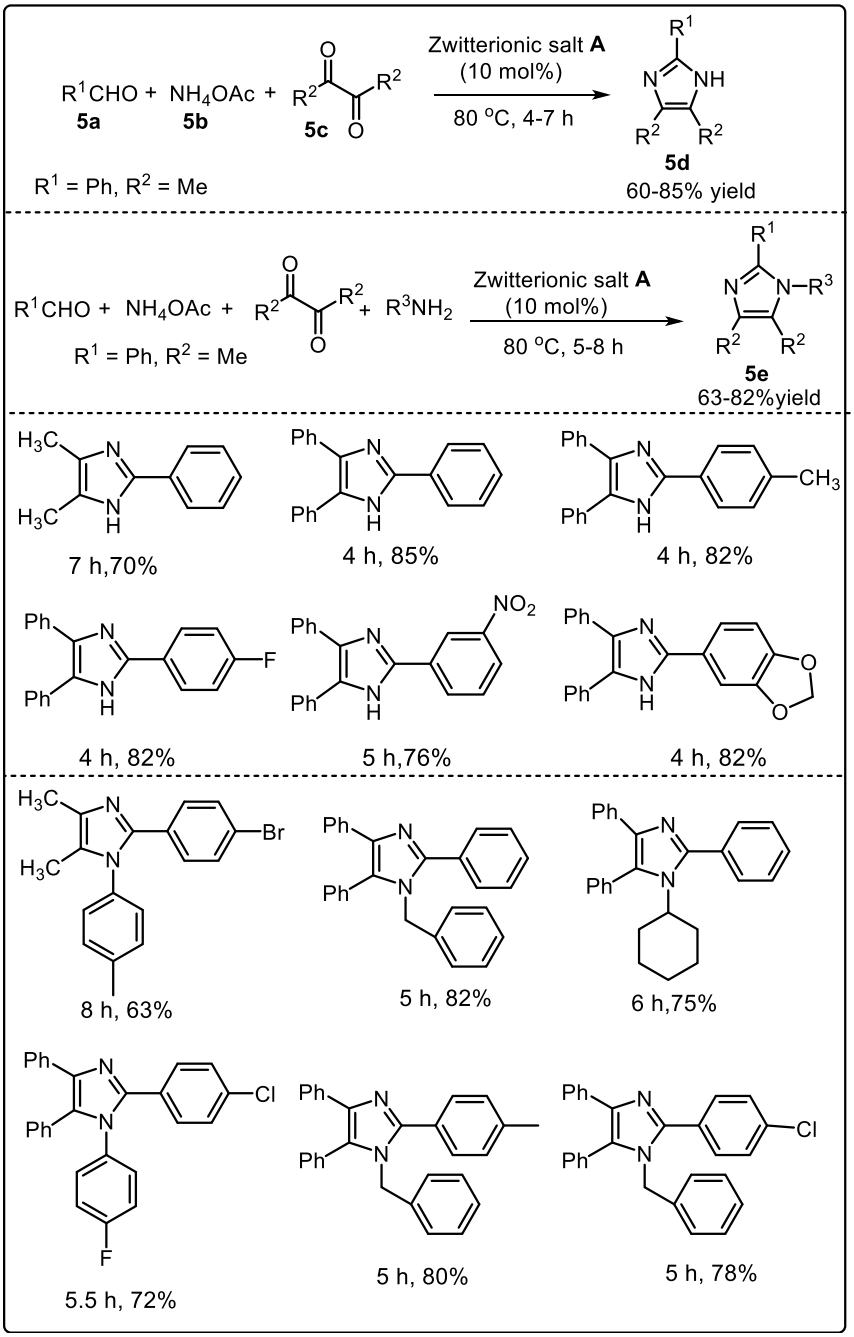

Figure 12.6: Zwitterionic type molten salt-catalyzed synthesis of tri- and tetra-substituted imidazole derivatives (Hajra method).

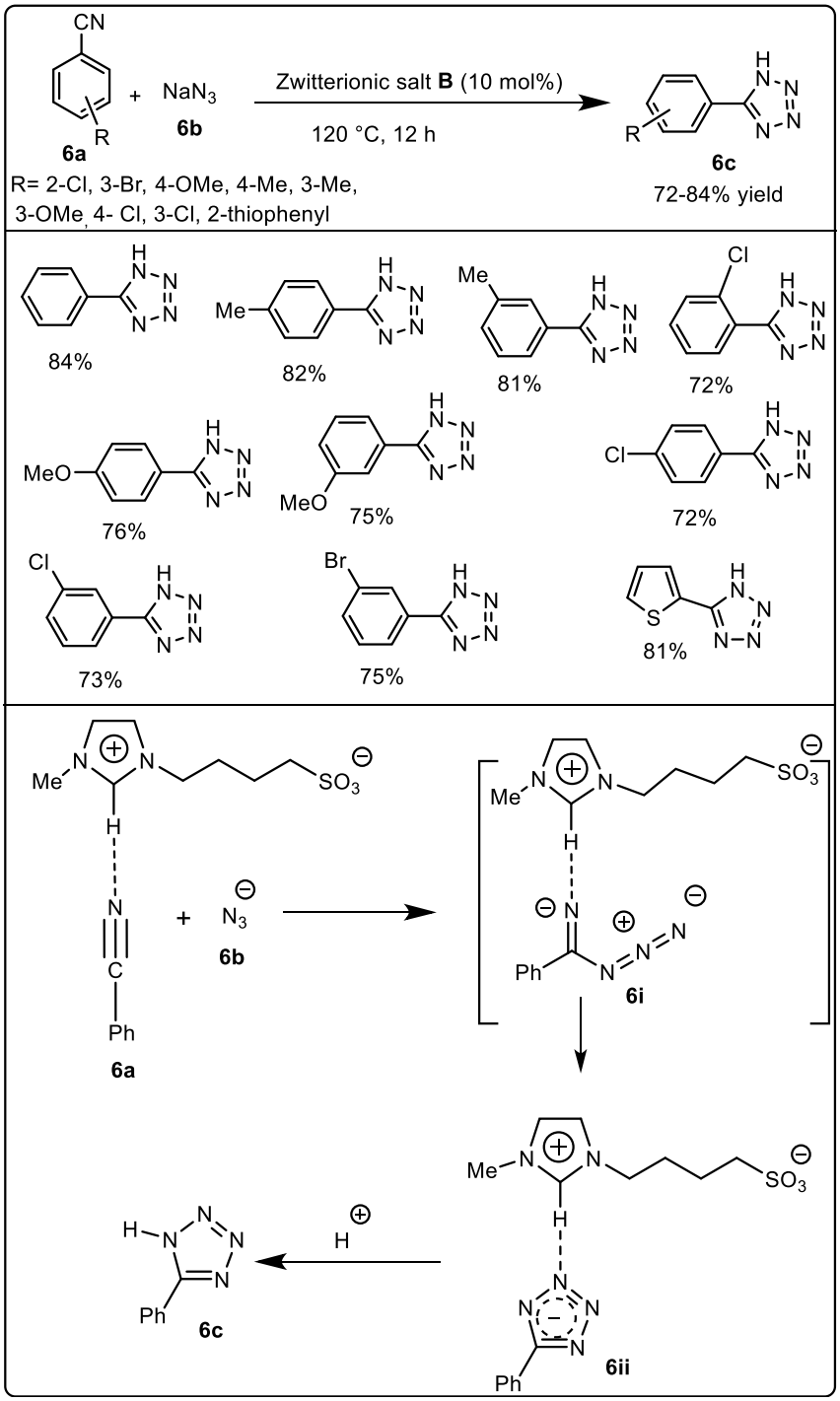

Figure 12.7: Zwitterionic type imidazolium molten salt-catalyzed synthesis of 5-substituted 1*H*-tetrazoles (Hajra method).

12.7 Synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones using zwitterionic type imidazolium molten salt catalysis

Zhou & Chen et al. [19] enlisted an Erlenmeyer type reaction using zwitterionic type imidazolium molten salt as a catalyst for synthesis of a series of azalactones **7c**. According to this method, 1 equiv. of aryl aldehyde reacted with 1.1 equiv. of hippuric acid in presence of 5 mol% imidazolium molten salt as catalyst and 5 equiv. of acetic anhydride at 60 °C for 3–6 h. The desired azalactones **7c** were achieved up to 89% yield (Figure 12.8). In this method, aromatic aldehydes having electron-withdrawing groups produced higher yields than that of aromatic aldehydes containing electron-donating groups. However, aliphatic aldehydes did not respond this methodology under the mentioned reaction conditions. Based on earlier reports and their findings, the authors proposed a reaction mechanism which is shown in Figure 12.8. At first, 2-phenyloxazol-5-one **7i** was formed by the intramolecular cyclization of **7b** in presence of acetic anhydride. In the meantime, imidazolium molten salt was activated by aldehydic carbonyl oxygen atom *via* H-bond formation to form the intermediate **7ii**. Next, **7ii** attacked the generated 2-phenyloxazol-5-one **7i** to afford another intermediate **7iii**. Finally, dehydration of **7iii** led to the final product **7c**.

12.8 Synthesis of 5,6-unsubstituted 1,4-dihydropyridines

In 2016, an easy and efficient methodology for the synthesis of 5,6-unsubstituted 1,4-dihydropyridine derivatives **8d** was developed by our group [20]. The reported three-component methodology used amines, β–keto esters, and α,β–unsaturated aldehydes as reactants under solvent-free conditions at room temperature. This reaction was also catalyzed by 10 mol% of imidazole-based zwitterionic salt. The desired product 5,6-unsubstituted 1,4-dihydropyridines were achieved up to 84% yield within just 1 h (Figure 12.9). The authors tested zwitterionic salts **C** and **D** and observed lower efficiency than that of **B**. Moreover, increasing catalyst loading did not improve the percentage yields of the desired products. Based on earlier reports, the most probable mechanistic path was proposed as shown in Figure 12.9. At first, amine and β–keto ester was activated through H-bond formation as shown in **8i**. Next, **8i** was transformed to enamine **8iii**. Next, the generated enamine **8iii** reacted with activated α,β–unsaturated aldehyde **8ii** to produce the desired 5,6-unsubstituted 1,4-dihydropyridine **8d** as the final product.

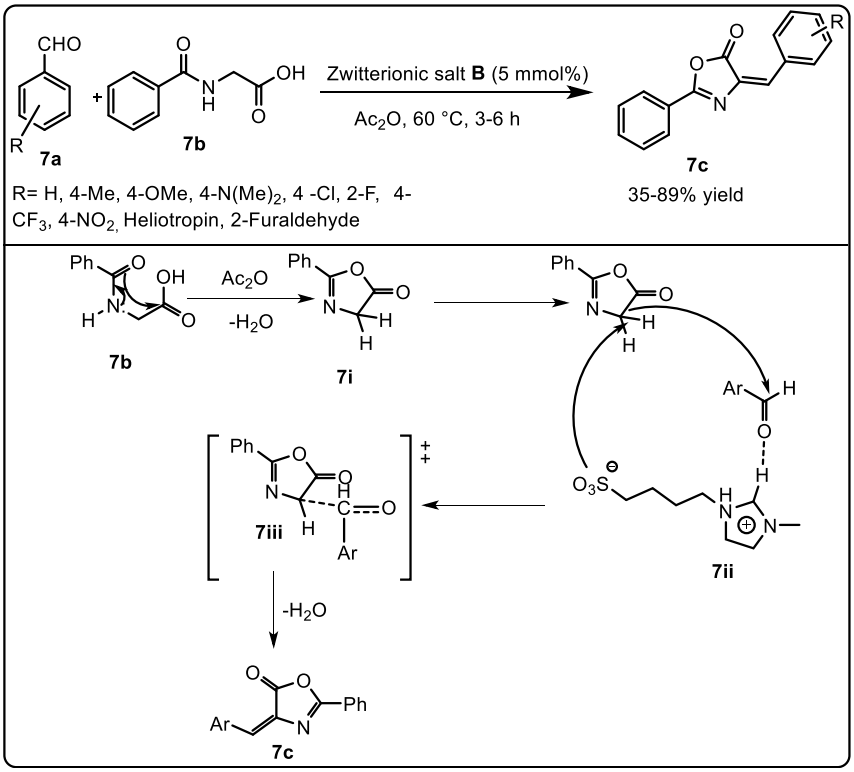

Figure 12.8: Zwitterionic type imidazolium molten salt catalyzed synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (Zhou & Chen method).

12.9 Regioselective ring-opening of aziridines

At around the same time, Majee et al. [21] developed an excellent regioselective ring-opening methodology for aziridines by using various nucleophiles like pyrrole, indoles, methanol, ethanol, di-iso-propylamine, and acetic acid under solvent-free conditions in presence of zwitterionic-type imidazolium molten salt **B** (Figure 12.10). The authors tested other zwitterionic molten salts, however, they were less efficient than that of **B**. Different aziridine systems with various substituted indoles were used to test the substrate scop for this methodology. It was observed that the electron-deficient as well as electron-rich indoles responded the reaction with various aziridines to generate the corresponding products with good yields under optimized reaction conditions. Moreover, *N*-substituted indole also reacted to this solvent-free ring-opening reaction and afforded corresponding products with satisfactory yields. In addition, ethanol, methanol, diisopropylamine, acetic acid, and pyrrole were also responded to the reaction and acted as nucleophiles. Based on control experiments and previous

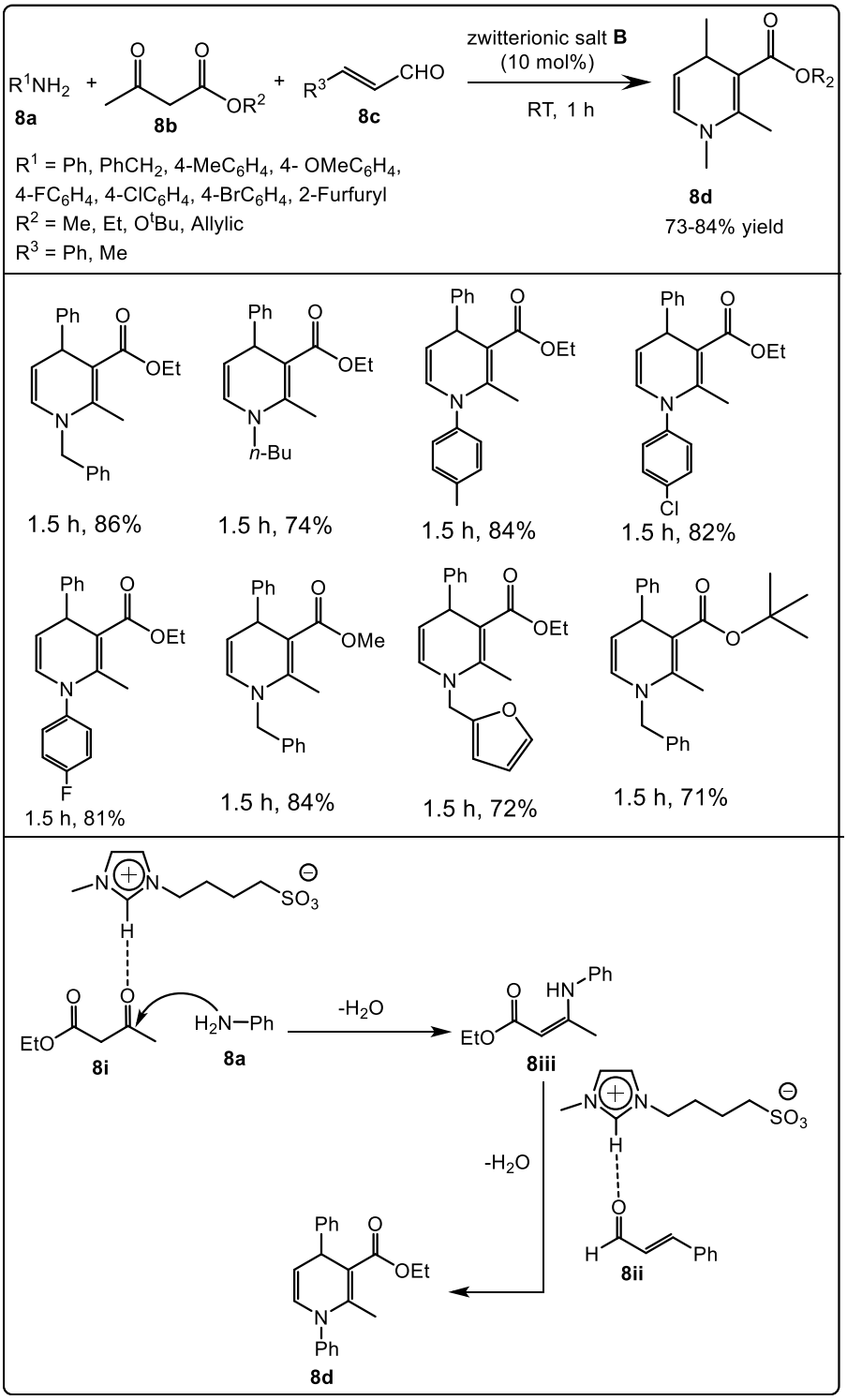

Figure 12.9: Zwitterionic type imidazolium molten salt-catalyzed synthesis of 5,6-unsubstituted 1,4-dihydropyridine derivatives (Hajra method).

literature reports, a reaction mechanism was proposed. At first, a hydrogen bond was formed between the nitrogen atom of aziridine group and C2–H of imidazolium cation and hence it was activated. Next, the nucleophile **9b** attacked the activated complex in an S_N^2 fashion to generate intermediate **9i**. Finally, **9i** was converted to the desired product **9c** (Figure 12.10).

12.10 Synthesis of dipyrromethanes and bis(indolyl) methanes by using imidazolium zwitterionic molten salt catalysis

Hajra, Majee and their coworkers [22] enlisted an expedient synthetic methodology of dipyrromethane and bis(indolyl)methane derivatives using imidazolium zwitterionic molten salt as a catalyst at room temperature under solvent-free conditions. In this methodology, 1 equiv. of aldehyde **10a** reacted with 2 equiv. of pyrrole or indole **10b** at room temperature in presence of 10 mol% of zwitterionic molten salt under neat conditions. The desired products i.e. dipyrromethanes and bis(indolyl)methanes **10c** were achieved up to 87% yield within 1 h (Figure 12.11). The authors then checked the substrate scope for this method. They found that a series of substituted aryl aldehydes responded the reaction under standard reaction conditions. Even, heteroaryl aldehydes and aliphatic aldehydes gave the corresponding products under optimized reaction conditions. Not only that, a bunch of pyrrole or indole also produced the desired products with good to excellent yields. The authors then performed a comparative study on using both pyrrole and indole in a same reaction and observed that pyrrole part gave desired product, while the indole part remained unreacted. A plausible reaction mechanism was proposed based on previous literature reports. Initially, the aldehyde **10a** reacted with **10b** in presence of zwitterionic molten salt to give the intermediate **10i**. After that, the zwitterionic salt was released from **10i** and generated the alcohol **10ii**. Next, the generated alcohol reacted with another molecule of indole in presence of same catalyst and afforded desired product **10c** *via* **10iii** formation (Figure 12.11).

12.11 Zwitterionic imidazolium salt-catalyzed tetrahydropyranylation of alcohols

Towards the synthesis of a complex organic molecule, protection of common functional groups for examples carbonyl, hydroxyl, amine, and carboxylic acid is often required. Protection of hydroxyl group by tetrahydropyranyl (THP) moiety is one among various suitable methods. Expectedly, extensive research has been done for the

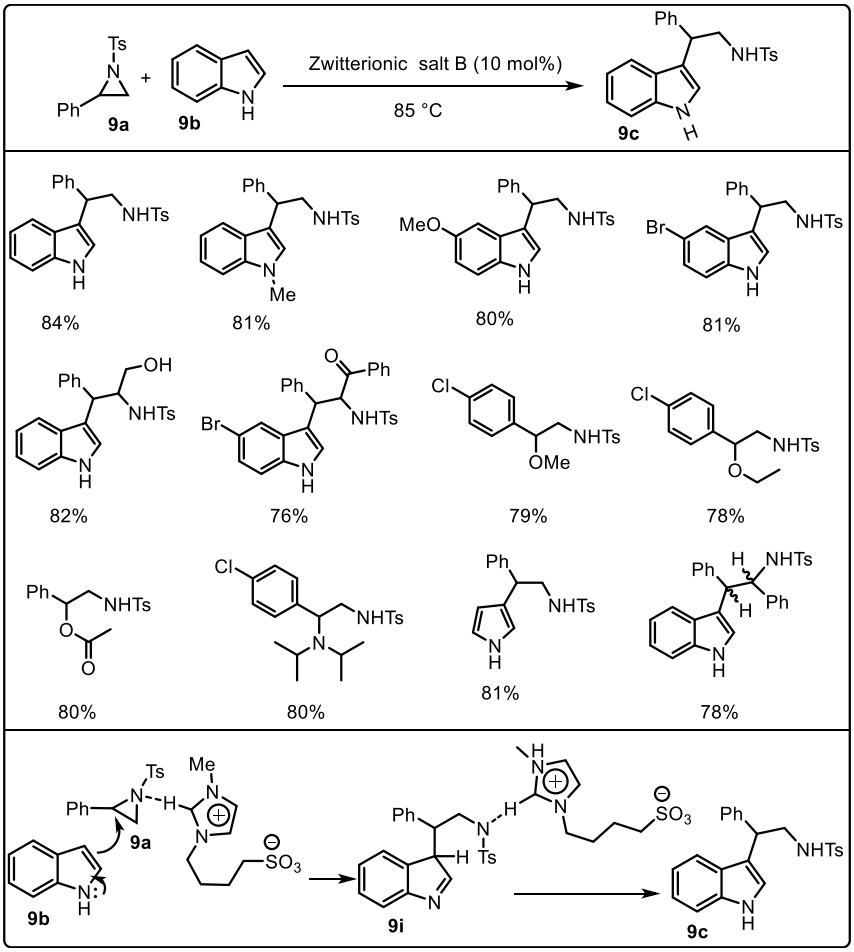

Figure 12.10: Zwitterionic type imidazolium molten salt-catalyzed regioselective ring-opening of aziridines (Majee method).

use of THP moiety as protecting group for hydroxyl group in the presence of catalytic amount of acids, Lewis acids, polyaniline salt, ferrous methanesulfonate, Bu_4NBr_3, $H_{14}[NaP_5W_{30}O_{110}]$, pyridinium chloride, Moβ, 2,4,6-trichloro[1,3,5]triazine, and using molecular iodine etc. However, considering green synthetic technique, the use of zwitterionic imidazolium salt under solvent-free conditions could be a good method of choice. In this circumstances, in 2017, Majee and coworkers [23] reported a suitable method for the protection of alcohols by THP moiety *via* the reaction of 3,4-dihydro-2*H*-pyran (DHP) and various alcohols in presence of 10 mol% of zwitterionic-type salt **A** as

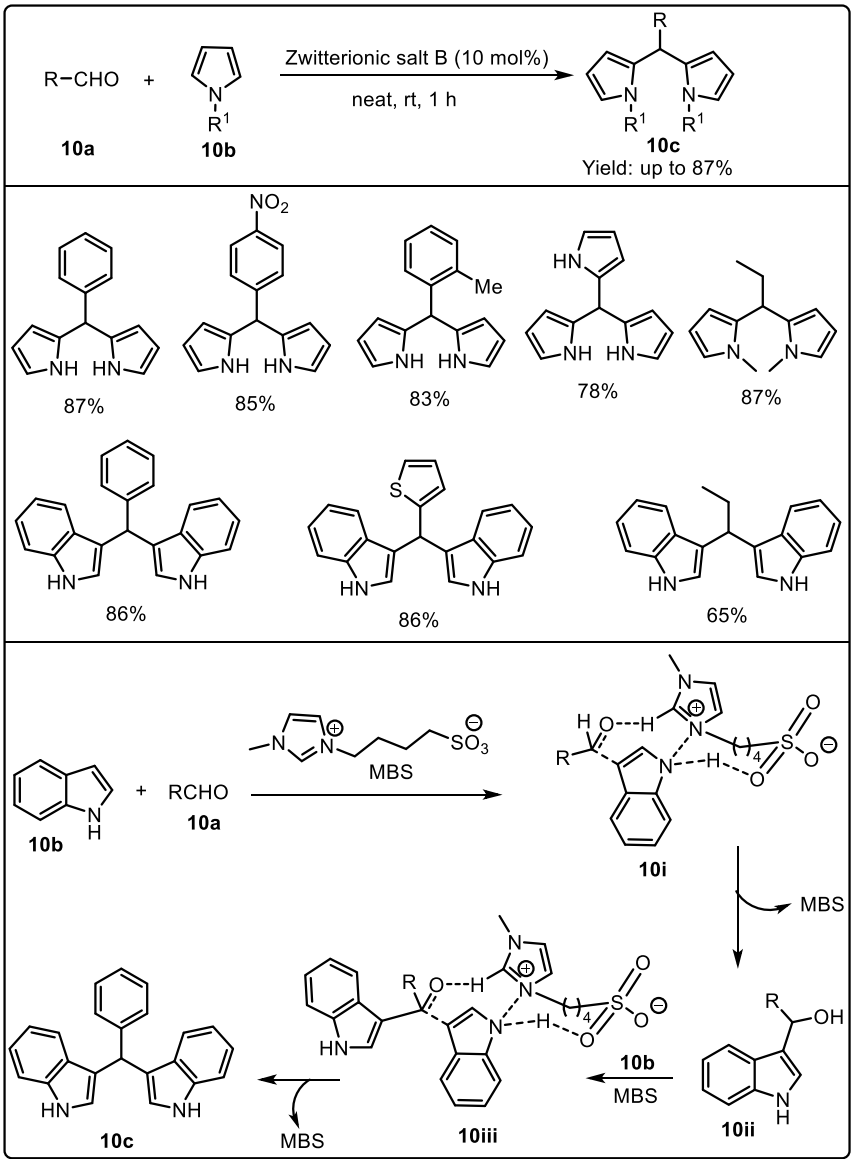

Figure 12.11: Synthesis of dipyrromethanes and bis(indolyl)methanes using imidazolium zwitterionic molten salt catalysis (Hajra and Majee method).

catalyst under mild and solvent-free conditions. The desired products were achieved with up to 94% yield within 10 h (Figure 12.12). Under optimized reaction conditions, the authors tested the effect of various aliphatic, saturated, and unsaturated alcohols as well as phenols. The corresponding products were obtained with good to excellent yields (70–94%).

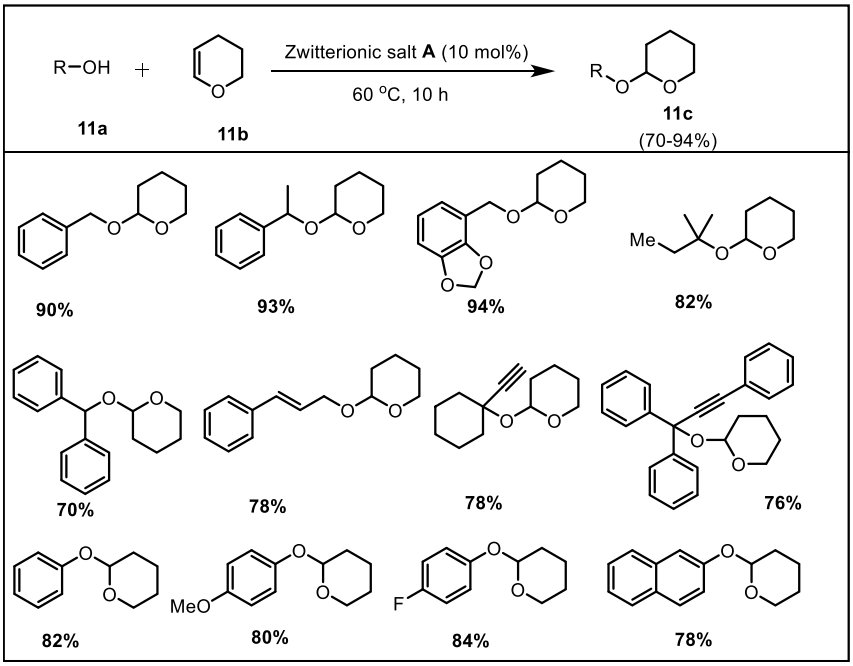

Figure 12.12: Zwitterionic salt-catalyzed tetrahydropyranylation of alcohols (Majee method).

12.12 Zwitterionic imidazolium salt-catalyzed synthesis of 4-hydroxy-3-thiomethylcoumarins

In recent years, 4-hydroxycoumarin and its derivatives have emerged as a vital synthetic intermediate for a wide range of natural products, drugs, pesticides and so on [24]. Among its derivatives, 3-substituted 4-hydroxycoumarins earned special attention due to its application in biological and medicinal fields. Therefore, a convenient and green synthesis of this compound is highly desirable. In this scenario, Majee and coworkers [25] very recently reported a mechanochemical fast and easy synthesis of 4-hydroxy-3-thiomethylcoumarins **12d** using imidazolium zwitterionic molten salt as catalyst under ball-milling conditions starting from 4-hydroxycoumarins, aldehydes, and thiols (Figure 12.13). Under the optimized reaction condition, the authors have first tested a series of aromatic, aliphatic as well as heteroaryl aldehydes, and thiols by the reaction with 4-hydroxycoumarin and achieved the corresponding 4-hydroxycoumarin derivatives in good to excellent yields (64–92%). Further, they examined substituted 4-hydroxycoumarins and found that these substrates were well tolerable under present mechanochemical conditions. It is important to note that the reaction was air and moisture tolerable and purification of the product was very simple. The crude product after the reaction was treated with a mixture of ethanol and hexane

and followed by recrystallization to obtain pure product. Based on the literature reports, the authors proposed a suitable mechanism for this reaction as shown in Figure 12.13. Initially, imidazolium-based zwitterionic molten salt simultaneously activated

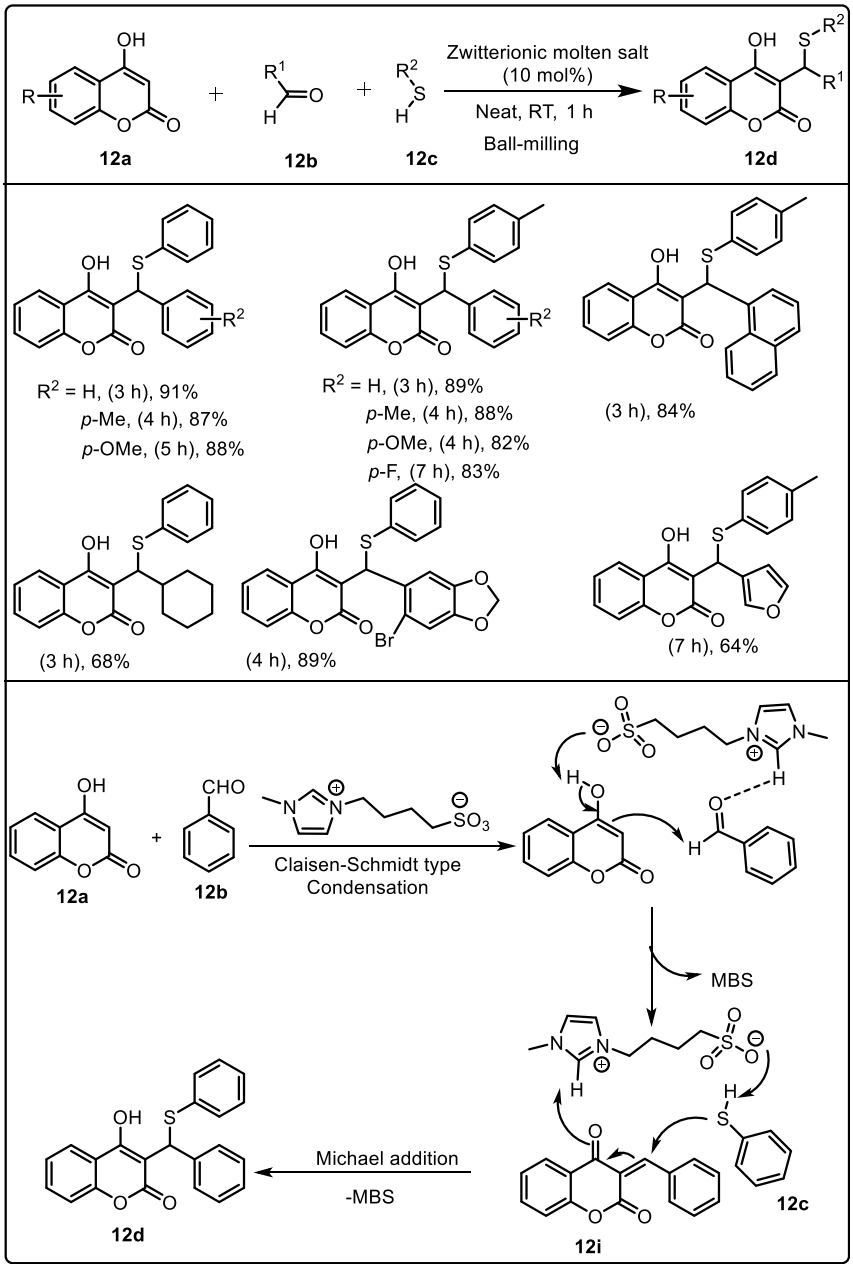

Figure 12.13: Zwitterionic imidazolium salt-catalyzed synthesis of 4-hydroxy-3-thiomethylcoumarins (Majee method).

4-hydroxycoumarin and benzaldehyde *via* its anionic part as well C2–H bond and this led to the Claisen–Schmidt-type condensation reaction generating the *α,β*-unsaturated ketone **12i**. The intermediate **12i** is a Micheal acceptor; thereby addition of thiophenol (donor) produced the final product **12d**.

12.13 Conclusion

Therefore, in this perspective, we have summarized the recent advances on zwitterionic imidazolium salt-catalyzed synthetic methodologies developed in the past few years. The zwitterionic imidazolium salts are extremely useful in synthetic chemistry for their simple preparation procedures, excellent yields formation, and easy to handle property. More interestingly, they are reused multiple times. No extra solvent is generally needed with them, which is an extra advantage of this catalyst. Above all, no costly and harmful metal is necessary with this catalyst and hence is highly environmental-friendly. In spite of all these elegant significances, zwitterionic imidazolium salts are not that much explored due to their insufficient knowledge of mechanism. Moreover, the preparation of chiral imidazolium-based molten salts and their application in asymmetric synthesis (for example, asymmetric Fischer esterification [26]) were rarely explored in the literature. Hence, there is lot more to explore on this green and clean technology. We hope this article will draw attention for a broad range of readership to dig deep inside this topic.

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Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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