Contents lists available at ScienceDirect

Arabian Journal of Chemistry

journal homepage: www.ksu.edu.sa

Review article

Organocatalyst as a synthetic gadget for pharmaceutically potent molecules

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ARTICLE INFO

Keywords:
Organocatalysts
Organo-photocatalyst
Bronsted acid/base catalysis
Lewis acid/base catalysis
Drug candidates

ABSTRACT

Organocatalysts have become a third main method of catalyzing chemical reactions aside from bio and metal catalysts. The potential for green chemistry and some striking benefits, including stability, low cost, easy availability, excellent enantioselectivity, and simple recovery, have made organocatalyzed reactions a fruitful approach. Recent developments in the field of organocatalysis include the enhancement of enantioselectivity, the development of novel catalyst classes such as NHCs, and dual catalysis, which combines organo- with metal or photocatalysis to enable novel reactivity. This review focuses on organocatalyzed chemical synthesis of pharmacophores such as benzoxazinones, pyrrolidines, triazoles, pyrazolinones, tricyclic coumarins, (+)-paroxetine, and (+)-femoxetine. The review has been outlined into six categories i.e. Lewis base catalysts, Lewis acid catalysts, Bronsted base catalysts, Bronsted acid catalysts, bifunctional catalysts, and organo-photocatalysts. Less reusability due to catalyst deactivation demands higher catalytic loading. Thus scalability in this field is still challenging. Moreover, achieving higher catalytic efficiency needs future efforts.

1. Introduction

Chemists can create new scaffolds with unique features and significant effects on human life by using the excellent toolkit that organic synthesis offers. Since Wöhler's urea synthesis, the discipline has fundamentally aided the medical sciences and seen enormous advancements in the synthesis of small to large compounds with natural origins (Garcia-Castro et al., 2016). Small organic molecules have the potential to significantly influence biology and medicine, serving as both pharmacophores and probes that help to elucidate the macromolecules controlling biological systems. Particularly, functionalized heterocyclic small molecules have been used in drug design applications in the pharmaceutical industry (Pitt et al., 2009). Both synthetic and naturally occurring biologically active products frequently contain heterocycles. Due to their ability to bind selectively to pharmacophores, their significance in drug development is continually growing. The majority of synthetic medicines in the market have a heterocyclic moiety (Baumann and Baxendale, 2013) which is synthesized by several traditional named reactions (Li, 2004). The majority of those traditional methods rely on the employment of high-boiling solvents, costly or hazardous catalysts, extended reaction durations, and thermal heating. To replace the antiquated classical methods that date back a long way, researchers from all around the world have devised alternative sustainable synthetic procedures (Taylor et al., 2016; Nishanth Rao et al., 2021).

According to the 1987 Brundtland Commission on Environment and Development of the UN (Brundtland, 1985), the term "sustainable development" refers to development that meets present needs without endangering the capacity of future generations to fulfill their necessities. Creating more renewable energy sources and lowering pollution are two of the most important components of sustainable development. The modern chemical industry faces a challenge in maintaining its socio-economic benefits and applications while protecting the environment. Synthesis of biologically active moieties by using organocatalysis reduces the environmental impact of chemical processes (Clark and Rhodes, 2007; Shaikh, 2014).

Organocatalysts have broad applications across multiple fields due to their efficiency, selectivity, and eco-friendly properties. They play a crucial role in drug discovery and asymmetric synthesis in the pharmaceutical sector, facilitating the synthesis of enantiomerically pure

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https://doi.org/10.1016/j.arabjc.2024.106027
Received 27 June 2024; Accepted 14 October 2024
Available online 22 October 2024

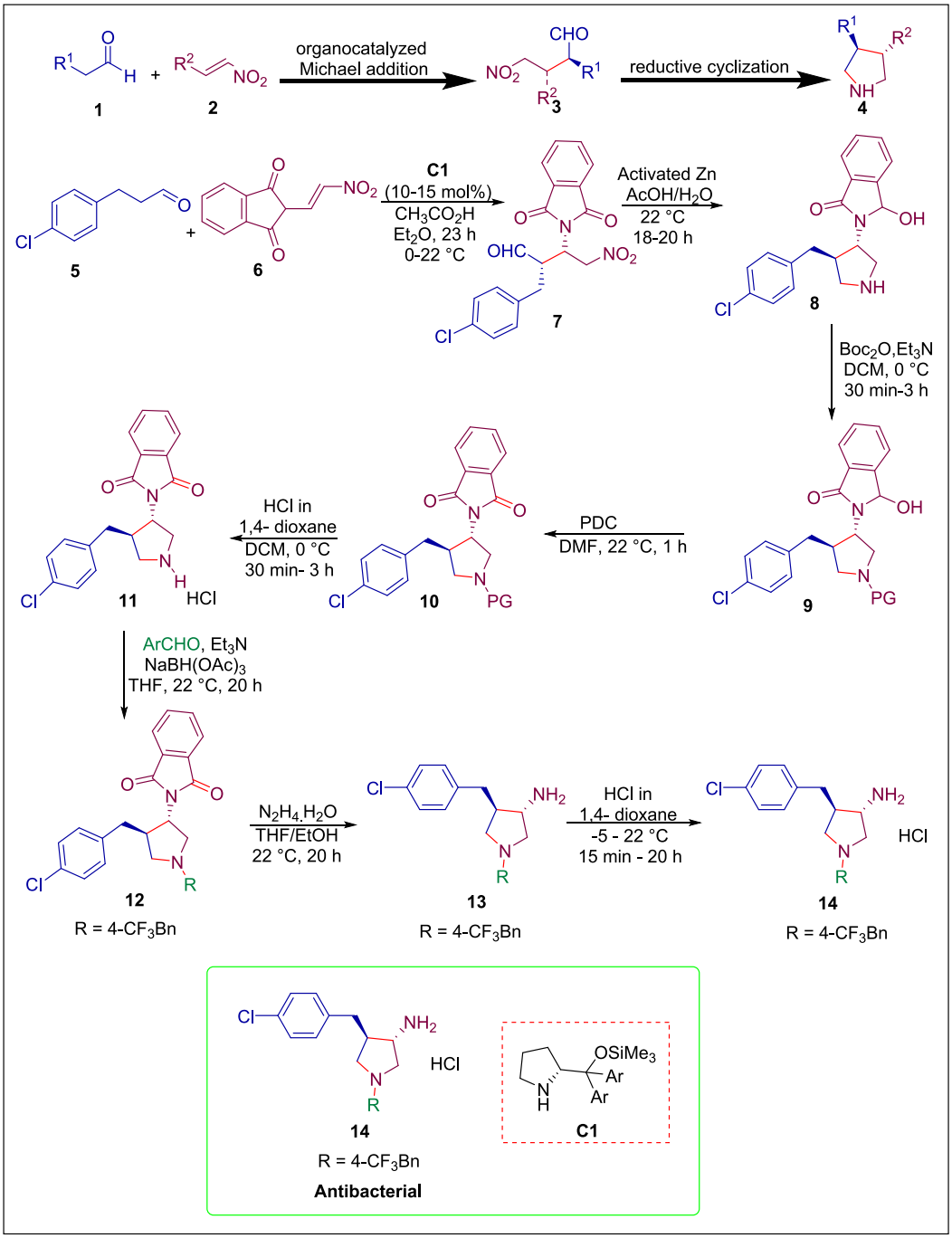
Table 1
Summary of the use of organocatalysts resulting in bioactive molecules.

Catalyst type	Catalyst name	Catalyst code	Synthesized compounds	Bioactivity	Reference
Lewis base catalysts	Hayashi-Jørgensen catalyst	C1	14	Antibacterial	(Rodriguez et al., 2020)
		C2	22-*trans*, 27-*trans*	Antidepressant	(Szcześniak et al., 2019)
		C3	31a	Anticancer	(Zhang et al., 2018b)
		C4	34a	Anticancer	(Li et al., 2019)
	N-heterocyclic carbene (NHC)	C5	38	Topoisomerase I inhibitor	(Zimmerman et al., 2020)
		C6	50a	Antiparasitic	(Coelho et al., 2019)
		C7	60	Antirheumatic	(Murugesh et al., 2020)
	Tert-leucinamide	C8	64	Precursor of vitamin B5	(Du et al., 2021)
	Trimethylimidazolidin-4-one hydrochloride	C9	70c	Anticancer	(Pham et al., 2020)
	Triphenylphosphine	C10	73	Antibacterial	(Gholami et al., 2019)
			74b	Antioxidant	
Lewis acid catalysts	Trimethylsilyl trifluoromethane sulfonate	C11	103	Anticancer	(Štadániová et al., 2020)
	Hyamine	C12	101, 102	Antibacterial	(Arora et al., 2018)
	Cinchonidine-derived quaternary ammonium	C13	111	Antiandrogenic	(Guerrini et al., 2014)
	Boron trifluoride diethyl etherate	C14	115	Anti-inflammatory, Treat sleeping sickness, Postsynaptic-selective alpha-1-antagonist	(Mahecha-Mahecha et al., 2020)
	Ethylaluminum dichloride	C15	120	Antiangiogenic and antioxidizing	(Wu et al., 2022)
Bronsted base catalysts	Pyrrolidine	C16	138	Antirenal fibrosis	(Simek et al., 2022).
		C17	151	Anticancer	(Zhang et al., 2019c)
		C18	153, 155	Anticancer	(Xu et al., 2019b)
			165	Anti-inflammatory	
		C19	167	Cathepsin K inhibitors	(Silva et al., 2020)
	DBU	C20	172, 174	Antifungal	(Khan and Saigal, 2018)
			177c	Antioxidant	(Gomes et al., 2020)
			179	Anti-HCMV	(Herrmann et al., 2023)
	Cinchona primary amine	C21	(±)-199	Antibacterial	(Ernouf et al., 2018)
		C22			
	Quinidine	C23	202	Anticancer	(He et al., 2022)
	Cinchonine-derived squaramide	C24	211	HRV protease inhibitors	(Wu et al., 2019)
	DABCO	C25	229	Ab 1-X inhibitor in PDAPP	(Winneroski et al., 2019)
			232	HIV-1 NNRTI inhibitor	(Chen and He, 2020)
	4-pyrrolidinopyridine	C26	239	Dithiolated *O*-antigen of *E. coli* serogroup 64	(Wan et al., 2023)
	TBD	C27	245	Photosensitizers in cancer therapy	(de Oliveira et al., 2019)
Bronsted acid catalysts	Takemoto's thiourea	C28	255	Treat Chagas disease	(Guerrero-Corella et al., 2021)
	Quinine-derived thiourea	C29	261a	Anticancer	(Wang et al., 2023)
		C30	264		(Li et al., 2023)
	Chiral phosphoric acid	C31	267	Antiviral and Anticancer	(Yan et al., 2022)
		C32	272	Anticancer	(Wang et al., 2022)
	α-angelica lactone	C33	277	Anti-platelet	(Thatikonda et al., 2020)
	DES	C34	290	Anti-inflammatory and Analgesic	(Imran et al., 2020)
	p-toluenesulfonic acid	C35	304,305	Potential enzyme inhibitors	(Repetto et al., 2019)
	Triflouoroacetic acid	C36	310a	Anticancer	(Srinivasulu et al., 2018)
	Pyridine-2-carboxylic acid	C37	321	AChE inhibitor	(Pervaiz et al., 2020)
Bifunctional organo-catalysts	Cinchona alkaloid catalyst	C38	324	Anticancer	(Liu et al., 2021)
	Cinchona-based thiourea	C39	332	Antidepressant and Antiparasitic	(Park et al., 2019)
	Cinchona alkaloids-derived squaramide	C40	340	Anti-proliferative	(Chang et al., 2022)
	Quinine	C41	343	Anticancer	(Hammer et al., 2018)
	Hydroquinine	C42	355	Anticancer	(Kovalevsky et al., 2023)
	Quinine-derived squaramide	C43	358	Anticancer	(Zhao et al., 2023a)
	Proline	C44	361	COX-2 enzyme inhibitor	(Akhtar and Lee, 2020)
	Prolinol	C45	375	SPHK inhibitors	(Escudero-Casao et al., 2018)
		C46	394	Antidepressant	(Sharma and Pandey, 2022)
	β-amino alcohol	C47	407	Dopamine agonists	(Chavan et al., 2019a)

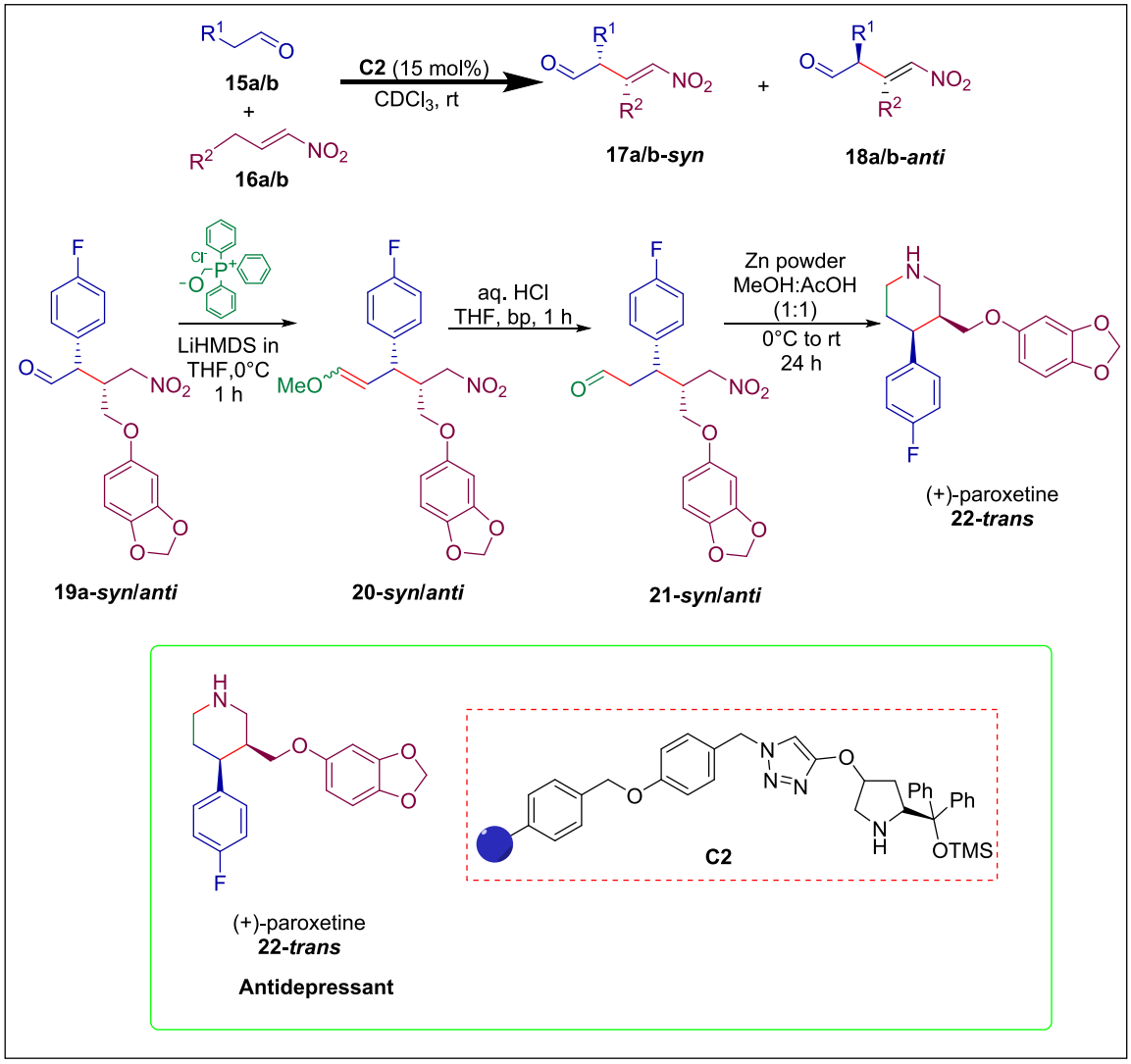
(*continued on next page*)

Table 1 (*continued*)

Catalyst type	Catalyst name	Catalyst code	Synthesized compounds	Bioactivity	Reference
	Chiral carbamate	C48	410	RNA polymerase inhibitor	(Gannedi et al., 2021)
Organo-photo catalysts	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene	C49	414	Anticancer	(Sherwood et al., 2018)
	CC-CMP	C50	424	Cholinesterase inhibitor, Antitumor and Treat glaucoma	(Ou et al., 2019)
	Lumiflavin	C51	431	Anti-convulsant, Thrombin inhibitor and Phosphodiesterase-4 inhibitor	(Chilamari et al., 2020)
	Anthraquinone	C52	437	Treat cardiovascular disease, Analgesic and Antimalarial	(Zhao et al., 2023b)
	Eosin Y	C53	444	Inhibitors of liver X receptor	(Vidyacharan et al., 2019)



Scheme 1. Hayashi-Jørgensen catalyzed the synthesis of pyrrolidine derivatives.



Scheme 2. Hayashi-Jørgensen catalyzed synthesis of (+)-paroxetine.

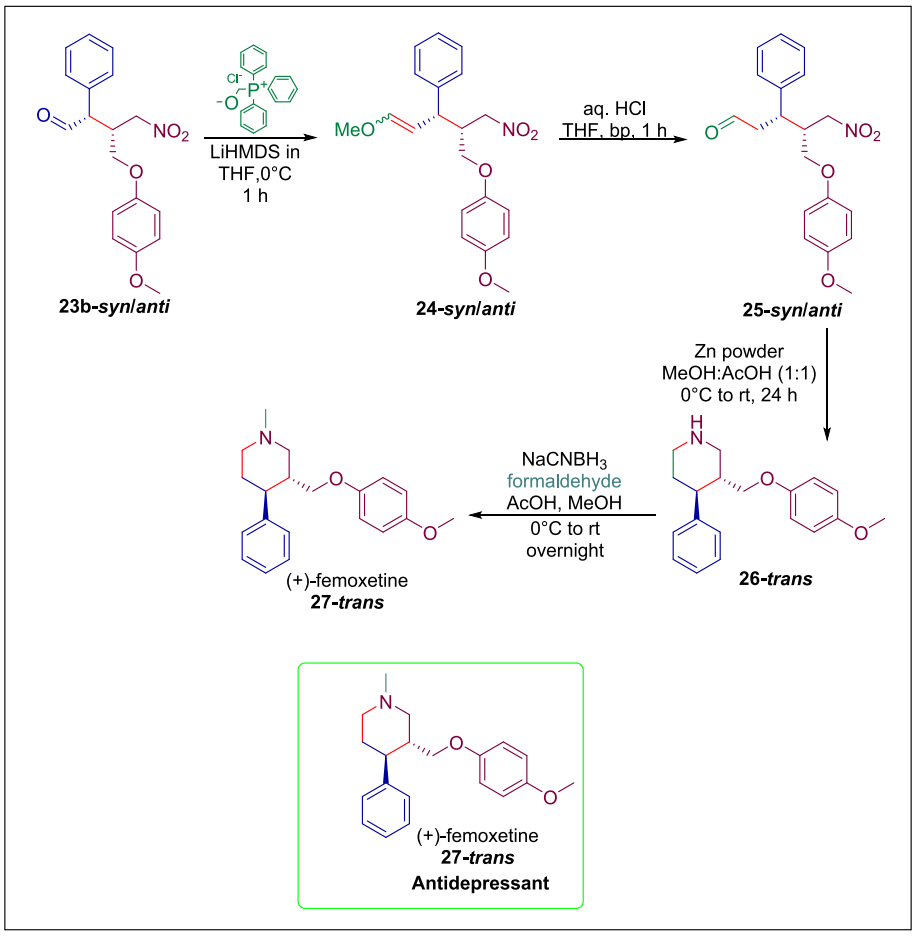
molecules (Burke, 2023). Organocatalysts help in the sustainable synthesis of green insecticides and agrochemicals in agriculture. They are also important in material science for synthesizing biodegradable polymers and nanomaterials. In fine chemicals, these catalysts enhance the production of fragrances and flavors, while in renewable energy, improve biofuel production. Furthermore, organocatalysts are essential to green chemistry since they support solvent-free and sustainable processes (Aukland and List, 2021).

Metal-catalyzed reactions offer a greater range of substrates, but they also come with certain disadvantages, including the high expense of catalyst synthesis and the potential toxicity of the metals to the products (List, 2007; Davies, 2013). In contrast to metals, organic compounds are more affordable, stable, non-toxic, widely accessible, and ecologically benign. Furthermore, compared to metal-catalyzed reactions, organocatalyzed reactions are less susceptible to the presence of air or water. As a result, these reactions have improved operational simplicity and reproducibility. Both metal and biocatalysts can be better substituted by organocatalysts with greater effectiveness.

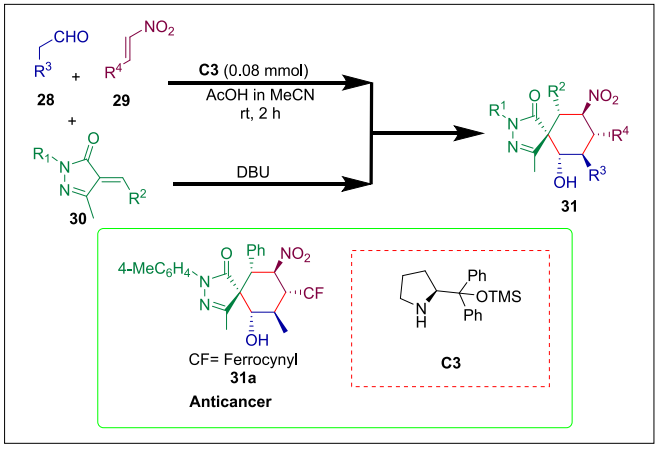
Unlike enzymes, that are extremely substrate-specific and cannot withstand even a slight alteration in the reactant's configuration, organocatalysts offer a wide range of substrates. Furthermore, an additional benefit that organic catalysts have over both metal and enzyme catalysts is the ease of amenability to solid support, which facilitates catalyst recovery and streamlines the reaction work-up process. Since enzymes are recognized because of high stereospecificity and strong catalytic activity, similar properties exhibited by tiny organic molecules have always been considered one of the reasons for their remarkable activity (Breslow, 1982). These organic compounds operate *via* interacting with substrates either through strong interactions like covalent bonding or weak interactions such as Van der Waals forces or H-bonding (Benaglia et al., 2003; Berkessel and Gröger, 2006; Barbas, 2008). The reaction rate is significantly accelerated as a result of these interactions (Akiyama et al., 2006; Taylor and Jacobsen, 2006). Even though organic molecules have long been employed as catalysts, it has only been in the last few years that the employment of these molecules in enantioselective synthesis has become a significant idea (Raj and Singh, 2009).

Recently Zafar *et al.* (Zafar et al., 2024) and Ahmad *et al.* (Ahmad et al., 2024)wrote reviews on the synthesis of organic compounds by using organocatalysts with focus on mechanistic studies. While this review majorly focuses on the pharamaceitical advantages of organocatalyzed reactions.

This review illustrates the synthesis of several bioactive molecules such as pyrrolidines, triazoles, pyrazolinones, tricyclic coumarins, (+)-paroxetine, and (+)-femoxetine by using different organocatalysts. It has been categorized into Lewis base catalysis, Lewis acid catalysis, Bronsted base catalysis, Bronsted acid catalysis, bifunctional catalysis, and organo-photocatalysis. These classes are further categorized based on the names of the organocatalysts that are used Table 1.



Scheme 3. Hayashi-Jørgensen catalyzed synthesis of (+)-femoxetine.



Scheme 4. Hayashi-Jørgensen catalyzed the synthesis of pyrazolone-ferrocene hybrids.

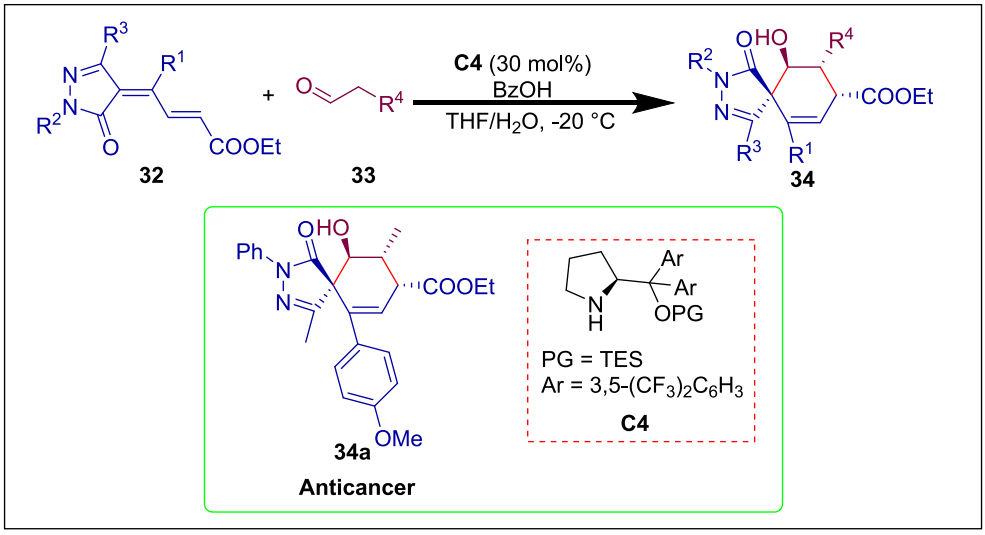
Remarkably, a large number of the very recently created asymmetric organocatalysis syntheses meet crucial requirements for a commercial process. In general, developing scalable catalyst preparation processes, further reducing catalyst loading, and technically appealing downstream processing methods will be major challenges to the greater usage of organocatalysts. Finding extremely appealing and cost-effective synthetic pathways to the target molecules, such as avoiding the use of protective groups (especially those with challenging cleavage), is another problem (Gröger, 2008).

2. Lewis base catalysis

Lewis bases organocatalysts based on nitrogen, carbon, oxygen, phosphorus, and sulfur make up the majority of organocatalysts. These bases react *via* a variety of processes to change substrates into either electrophiles or activated nucleophiles. Iminium ions, enamines, acyl ammonium ions, 1-, 2-, or 3-ammonium enolates, etc. are examples of typical reactive intermediates (Seayad and List, 2005). Moreover, Lewis base organocatalysis includes the enolate reaction modes of ammonium (Gaunt and Johansson, 2007)and azolium (Douglas et al., 2012), which employ *tert*-amine or NHC catalysts, respectively (Douglas, 2012). Lewis base catalysis has several benefits, including mild reaction conditions, metal-free residue, and environmental friendliness (Meng et al., 2022). In 2018, Li and colleagues synthesized the annulated 4*H*-pyran and annulated 3, 4-dihydro-2*H*-pyran by a TEDA-promoted chemo-divergent (4 + 2) cycloaddition reaction of allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones (Xi et al., 2018). Afterward, the authors discovered that the same materials could be used to form a formal (3 + 2) cycloadduct under phosphine catalysis (Ma et al., 2019).

2.1. Hayashi-Jørgensen catalyst

Pyrrolidine derivatives show potent antimicrobial activities (Le Goffic, 1985; Raj et al., 2003). Le Goffic established that pyrrolidine moiety boosted lincosamide drugs' antibacterial action (Le Goffic, 1985; Odagiri et al., 2013). Pyrrolidine cores are synthesized by various synthetic methods, including reductive amination and dipolar cycloadditions of azomethine ylides (Bdiri et al., 2017). Nevertheless, organocatalyzed Michael additions are one of the strongest and most



Scheme 5. Hayashi-Jørgensen amine-catalyzed synthesis of spirocyclohexene pyrazolones.

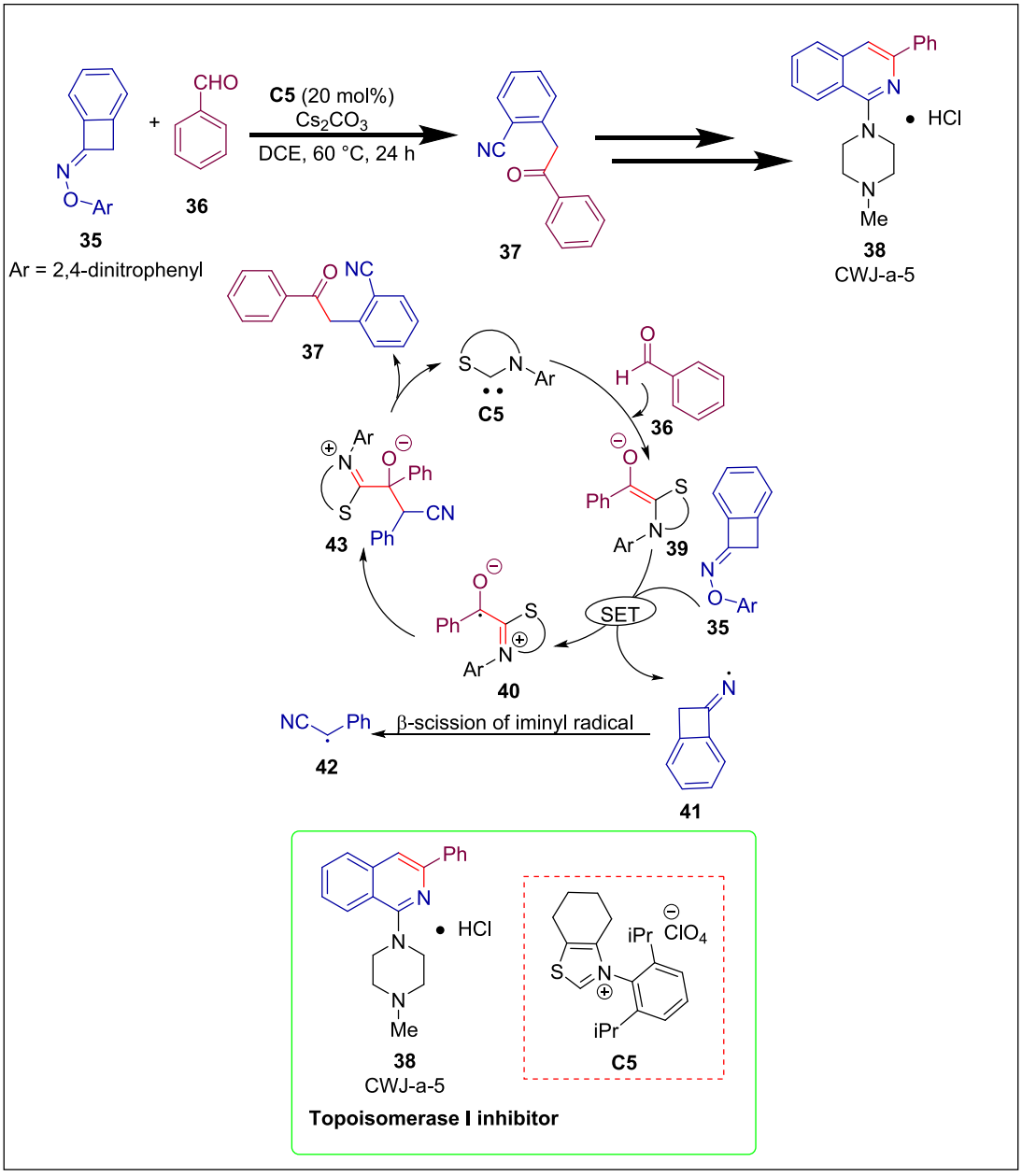
reliable techniques. Rodriguez et al. used organocatalytic Michael addition and reductive cyclization to synthesize a library of 3,4-disubstituted pyrrolidine derivatives. First, aldehyde **5** and nitroalkene **6** undergo Hayashi-Jørgensen **C1** catalyzed Michael addition to give the Michael adduct **7**, which then goes through reductive cyclization, reducing one carbonyl group in the isoindoline-1,3-dione scaffold to produce pyrrolidine **8**. The Tertbutoxycarbonyl group protects the secondary amino group of pyrrolidine **8**, resulting in Boc-protected pyrrolidines **9**. Then 3-hydroxyisoindolin-1-one moiety of compound **9** is oxidized to isoindoline-1,3-dione moiety to give product **10** which undergoes reductive amination to afford corresponding benzyl derivatives **12**. These derivatives undergo hydrazinolysis to give **13** (Scheme 1) (Rodriguez et al., 2020). Hydrochlorides **14** of these products **13** are produced to improve their solubility in aqueous solutions for biological testing. The key features of this methodology are that only one-column chromatography is required for this four reaction steps sequence, the catalyst is readily available, stable and typically shows constantly good catalytic activity, and the solvent Et_2O preserves good enantiomeric and diastereomeric purities. The synthesized compounds were tested for methicillin-resistant strains of *S. aureus* and *E. coli* bacteria. Compound **14** was shown to be the most effective with MIC_{100} = 37 μmol/L and MIC_{50} = 17 μmol/L respectively for both bacteria.

(+)-Paroxetine and (+)-femoxetine are used to treat depression. Their synthesis is frequently achieved using enzymatic asymmetric desymmetrization, asymmetric catalysis, chiral pool, chiral base, and chiral auxiliary (Greenhalgh and Simpkins, 2002; Gill et al., 2003). These techniques have shown to be successful, but their primary flaw is the lengthy and intricate synthetic sequencing. Szcześniak *et al.* devised a method for the asymmetric formation of these antidepressants by employing organocatalytic Michael addition of aldehydes to *trans*-nitroalkenes achieved in bath or continuous flow. The synthesis starts when aldehydes **15a/b** and nitroolefins **16a/b** undergo a Michael addition reaction in the presence of Hayashi-Jørgensen catalyst **C2** in a continuous flow to give the γ-nitroaldehyde **19a-*syn/anti*** which undergoes Wittig olefination to form the product **20-*syn/anti***. After that, olefin **20-*syn/anti*** is hydrolyzed to produce aldehyde **21-*syn/anti***, which is then subjected to reductive cyclization to produce paroxetine **22-*trans*** (Scheme 2) (Szcześniak et al., 2019).

(+)-Femoxetine's **27-*trans*** synthesis is carried out using the same chemical process. The crude mixture of γ-nitroaldehyde **23b-*syn/anti*** is subjected to Wittig olefination, producing compound **24-*syn/anti***, which, upon acidic hydrolysis, provides δ-nitroaldehyde **25-*syn/anti***. Without purification, this reaction was then employed directly for the subsequent step. After that, δ-nitroaldehyde **25-*syn/anti*** is treated with zinc powder to produce **26-*trans***, which is then treated with formaldehyde and $NaCNBH_3$ to produce (+)-femoxetine **27-*trans*** (Scheme 3). This method's simple procedure and use of an affordable, easily accessible substrate are among its main advantages.

An organometallic framework called lipophilic "sandwich" ferrocene is frequently used in the synthesis of anti-parasitic, antibacterial, and antitumor medicines (Hillard et al., 2010). Bioactive ferrocenes that have been synthesized through different techniques in the past few years can be either achiral or racemic or simple conjugates of ferrocenyl that already have chiral moiety (Van Staveren and Metzler-Nolte, 2004). The stereoselective construction of ferrocene compounds with potential applications in pharmacology has received relatively little attention. Zhang *et al.* used organocatalytic [2 + 2 + 2] annulation to create a series of chiral spirocyclic pyrazolone-ferrocene hybrids with numerous stereocenters in high yields and exceptional diastereo- and enantioselectivity. Aldehyde **28** and nitroalkene **29** undergo Hayashi-Jørgensen secondary amine **C3** catalyzed Michael addition. Subsequently, spirocyclic pyrazolone-ferrocene hybrids **31** are produced by adding compound **30** and DBU (Scheme 4) (Zhang et al., 2018b). This method is atom-economic, safe for the environment, and works well with many functional groups. Compound **31a**, found in this series, exhibited strong inhibition of RalA, with an IC_{50} of 1.20 ± 0.19 μM. It also caused reactive oxygen species to accumulate and prevented the growth of pancreatic cancer cells with IC_{50} = 1.6 μM.

Multifunctional spiropyrazolones fused with cyclohexane(ene) have appealing biological actions like antibacterial, anticancer, anti-inflammatory, and analgesic characteristics. Previously, asymmetric organocatalytic processes were used to create spiropyrazolone scaffolds from Pyrazolin-5-one substrates; however, in these methods, pyrazolinones function as adaptable electrophilic C2 synthons (Zheng et al., 2015b Li et al., 2016; Leng et al., 2018). Li *et al.* developed an asymmetric [4 + 2] annulation method using the *α,β,γ,δ*-unsaturated pyrazolone substrate **32,** aldehyde **33** and a Hayashi-Jørgensen amine catalyst **C4** to synthesize *α,β,γ,δ*-unsaturated pyrazolone **34**. The compound **33** is activated in this reaction using a HOMO-raising approach (Li et al., 2012; Li et al., 2018), while pyrazolone substrate **32** functions as the electron-deficient C4 scaffold and branched diene for spiro-construction (Li et al., 2018) (Scheme 5) (Li et al., 2019). Theafforded chiral compounds exhibited strong cytotoxic activity. The compound **34a** caused apoptotic cell death in HCT116 colorectal cancer cells and has IC_{50} = 0.37 μM.

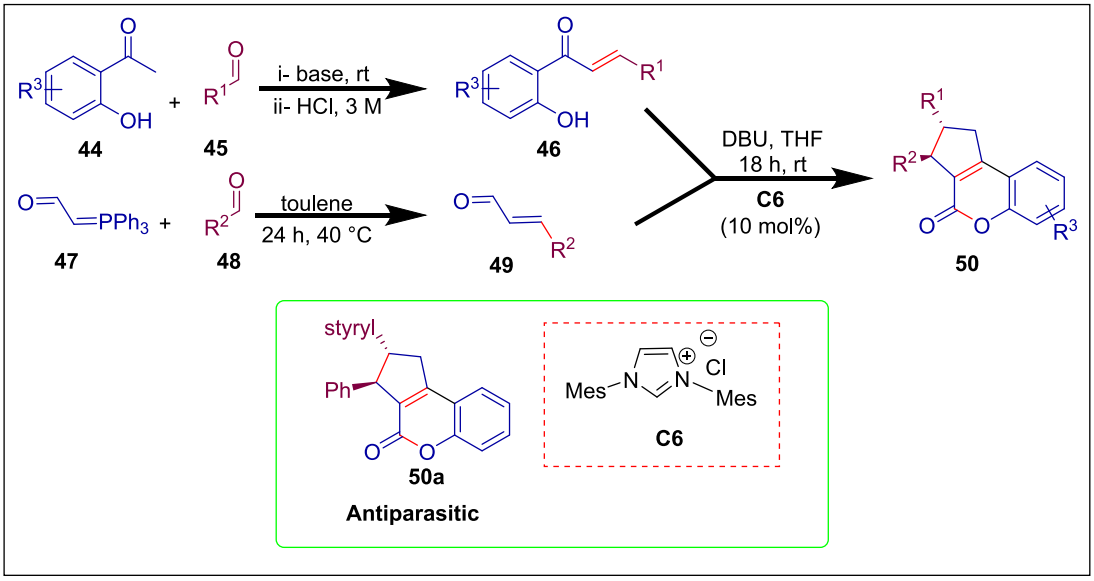


Scheme 6. NHC catalyzed synthesis of CWJ-a-5.

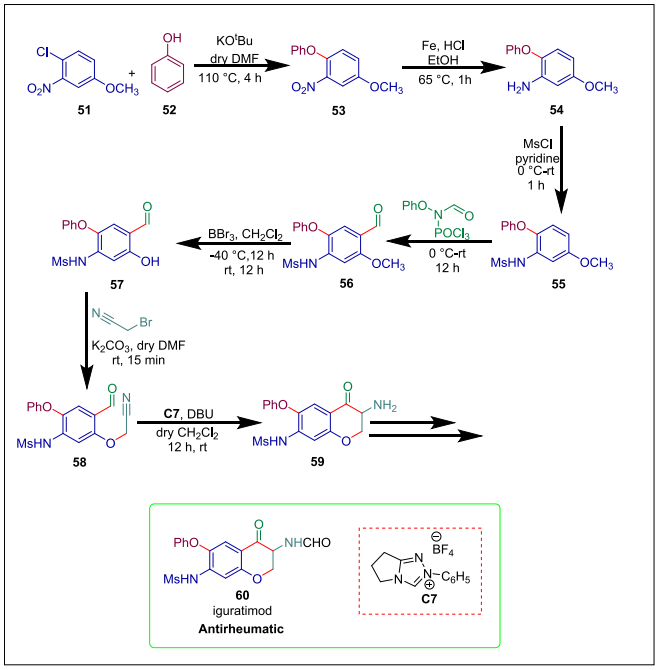
2.2. *N-heterocyclic carbene catalyst (NHC)*

Ketonitrile, a vital framework of numerous *N*-containing bioactive compounds like piperidine, pyridine, pyridin-2(1*H*)-one, and 2-aminothiophene, is produced *via* *N*-heterocyclic carbene catalyzed ring-opening coupling between an aldehyde and a cyclic oxime derivative in the presence of the NHC catalyst (Streuff et al., 2012; Nguyen et al., 2020). The problem of employing hazardous transitional metals in C–C bond activation has led to the development of this NHC-catalyzed approach. Yang and Wan developed thiazolium **C5** catalyzed reaction between oxime derivative **35** with benzaldehyde **36** to produce ketonitrile **37** which was then transformed into CWJ-a-5 **38**. Adding NHC **C5** to benezenecarbaldehyde **36** in the presence of Cs_2CO_3 initiates the catalytic cycle. The obtained intermediate **39** goes through a single-electron transfer process with cyclic oxime ether **35** to give the intermediates **40** and **41**. In iminyl radical **41,** the hyperconjugation effect between the unpaired-electron-occupied orbit on the *N* atom and the σ orbital of the *α*-C–C bond leads to a quick radical-type ring-opening process, yielding the nucleophilic alkyl radical **42**. Then the cross-coupling between **42** and **40** affords the compound **43**, which experiences an intramolecular fragmentation to furnish the desired compound **37** and regenerates the **C5** (Scheme 6) (Yang and Wan, 2021). This technique showed several good synthetic properties, including as high yields, readily available reactants, and environmental friendliness (Zimmerman et al., 2020). A formal synthesis of the strong topoisomerase I inhibitor CWJ-a-5 **38** demonstrates the synthetic potential of this new technique.

Chagas disease, which affects around 8 million individuals worldwide, is brought on by infection with the protozoan parasite *Trypanosoma cruzi*. There are currently only two medications that are approved to cure Chagas disease: nifurtimox (NFX) and benznidazole (BZ). Both medications show poor chronic phase cure rates and frequently cause major side effects (de Fátima Oliveira et al., 2008). Coelho *et al.* synthesized eighteen tricyclic coumarins using NHC organocatalysis to fill this gap in novel drug candidates for Chagas disease. The first step in the synthesis of target compound **50** is to prepare *α*; *β*-unsaturated



Scheme 7. NHC catalyzed synthesis of tricyclic coumarins.



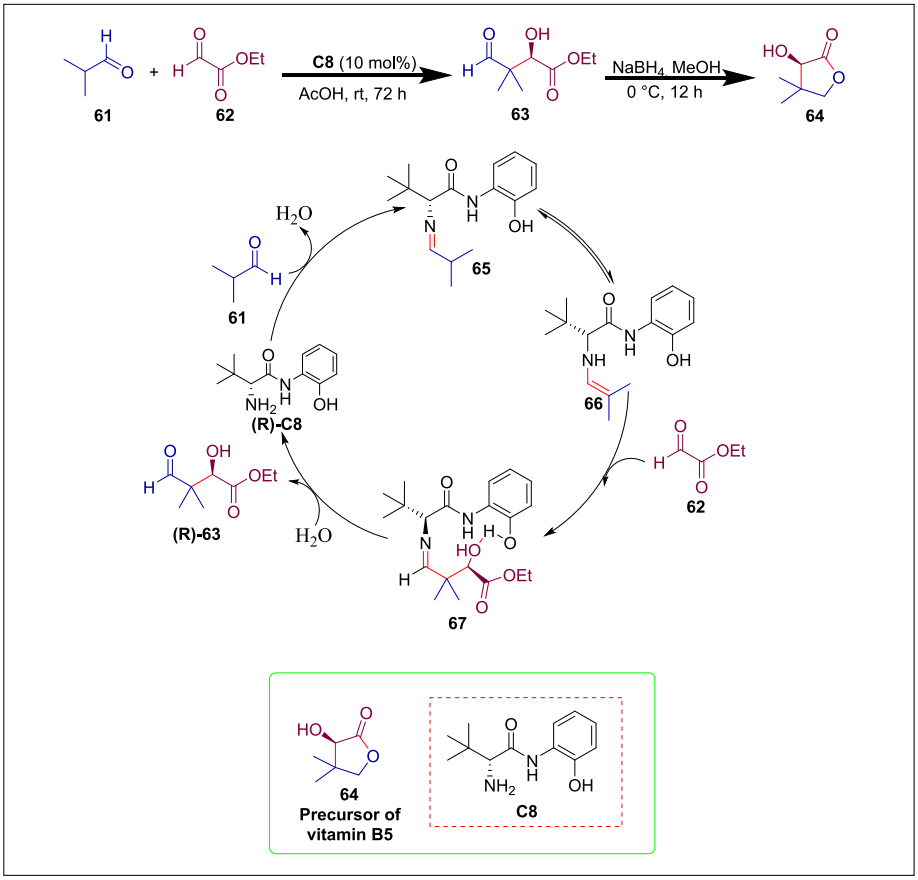
Scheme 8. NHC catalyzed synthesis of iguratimod.

aldehydes **49** using the Wittig reaction, which produces substituted cinnamaldehydes in a high yield. Cross-aldol condensation between aromatic aldehydes **45** and substituted 2-hydroxyacetophenones **44** yields the required chalcones **46**. The next step is a homoenolate annulation reaction between cinnamaldehydes **49** and chalcones **46**, which is catalyzed by NHC **C6** and results in good to outstanding yields of tricyclic coumarins **50** (Scheme 7) (Coelho et al., 2019). The cytotoxic efficacy of these synthesized compounds against *Trypanosoma cruzi* on L929 cells of mice was assessed. Ten of the eighteen compounds that were examined had IC_{50} values that were lower than those of the reference drug benznidazole. **50a** with IC_{50} = 0.4 μM was the most potent compound.

A synthetic drug called iguratimod (T-614) treats rheumatic diseases (Tanaka et al., 2015). It also lessens severe pancreatitis by blocking the NLRP3 inflammasome and the NF-kB pathway (Hou et al., 2019; Ishikawa and Ishikawa, 2019). Previously Takano et al. synthesized T-614 amine precursor utilizing 3-nitro-4-phenoxyphenol through NO_2 reduction, mesylation, *O*-alkylation using 3-chloropropionic acid, intramolecular ring closure using polyphosphoric acid, bromination, nucleophilic azidation and dehydrogenative amination. The overall yield under these protocols was unsatisfactory. Murugesh *et al.* devised a proficient synthetic technique to synthesize iguratimod **60** with high yield through regioselective Vilsmeier-Haack formylation and intramolecular *N*-heterocyclic carbene-catalyzed aldehyde-nitrile cross-coupling reactions. The first step of this synthesis is the nucleophilic aromatic substitution (SNAr) of 1-chloro-4-methoxy-2-nitrobenzene **51** with C_6H_5OH **52** to yield 4-methoxy-2-nitro-1-phenoxybenzene **53** which then goes through NO_2 reduction followed by mesylation to afford *N*-(5-methoxy-2-phenoxyphenyl) methanesulfonamide **54**. Then **54** undergoes Vilsmeier-Haack formylation and demethylation to yield *N*-(4-formyl-5-hydroxy-2-phenoxyphenyl)methanesulfonamide **57** which undergoes classical *O*-alkylation to give compound **58** that is converted into amine precursor of iguratimod **59** *via* aldehyde-nitrile cross-coupling using triazolium pre-catalyst (Scheme 8) (Murugesh et al., 2020).

2.3. Tert-leucinamide catalyst

(*R*)- pantolactone is an essential component of medicines and is the synthetic precursor of vitamin B5, often known as calcium pantothenate (Müller et al., 2000). Previous strategies for catalytic asymmetric transformations include the aldol transformation between silyl ether of *S*-ethyl 2-methylpropanethioate and isobutyraldehyde, as well as the chiral ligand–metal complex-catalyzed asymmetric reduction of keto-pantolactone, (Takahashi et al., 1986)a five-step process bearing on Sharpless dihydroxylation, (Upadhya et al., 1999)and an aldol transformation of ketopantolactone (Evans et al., 2002). Harmful transition metals, very low reaction temperatures (−78 °C), poor yields, and high costs of reactants are the main drawbacks of these techniques. Du *et al.* described *tert*-leucine-based 2-phenolic anilide **C8** catalyzed asymmetric cross-aldol reactions between glyoxylate **62** and aldehydes **61** to produce (*R*)-pantolactone **64**. The process begins when isobutyraldehyde **61** and phenolic tertiary-leucinamide catalyst **C8** combine to generate intermediate imine **65**, which reversibly transforms into intensely nucleophilic enamine **66**. To efficiently activate the aldehyde scaffold and quicken the aldol reaction, the catalyst's amide and hydroxy groups



Scheme 9. *Tert*-leucinamide catalyzed synthesis of (*R*)- pantolactone.

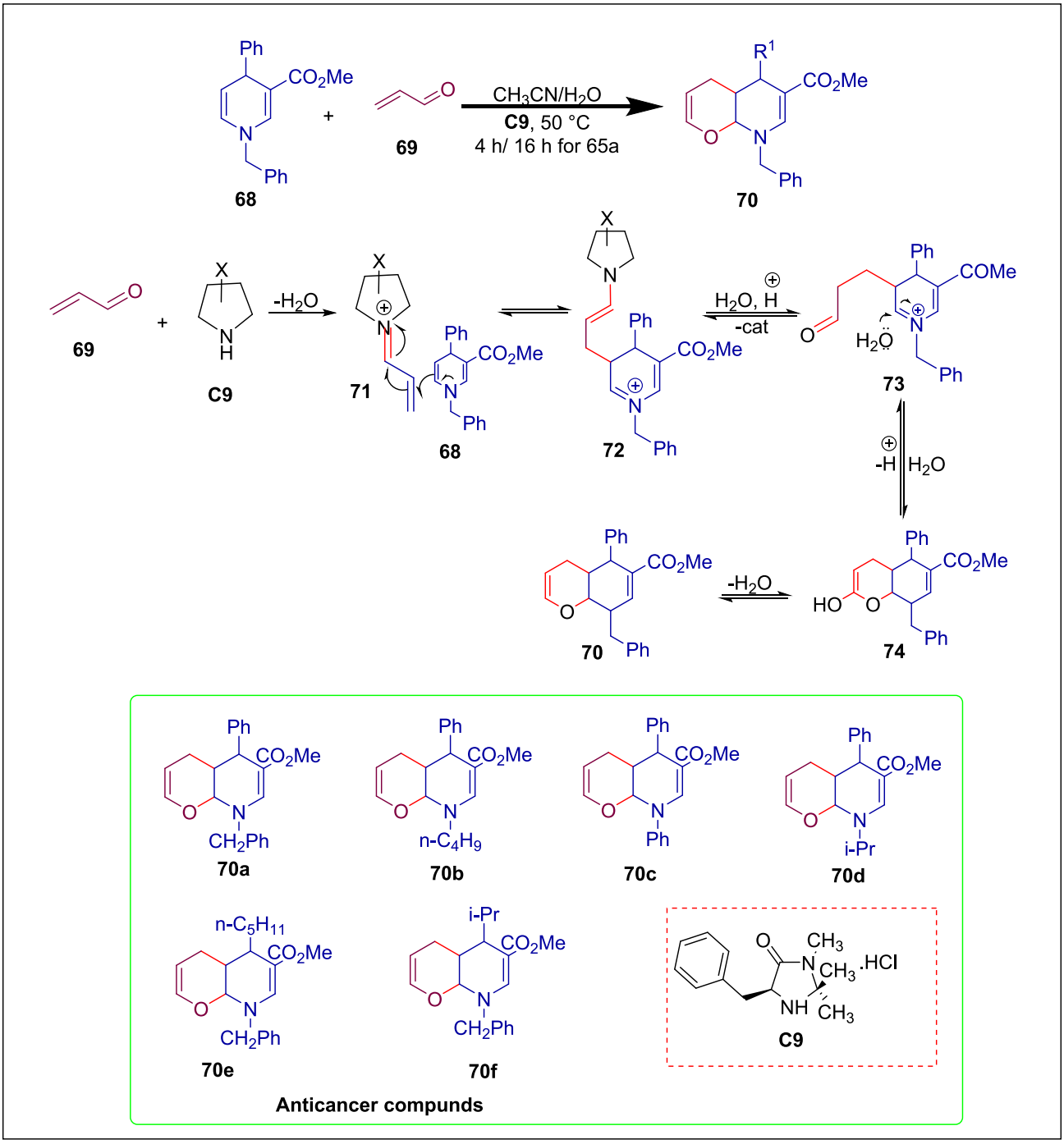
create two H-bonds with ethyl glyoxylate **62**. The bulky tertiary-butyl group of **C8** acts as a steric hindrance, so enamine's **66** attack to the **61** primarily occurs in the *Re*-face of the aldehyde skeletal of **62**. This results in the *R* configurational aldol product **63**, which is then reduced and immediately lactonized to produce (*R*)-pantolactone **64** in a high yield (Scheme 9) (Du et al., 2021). A simple recrystallization can easily enrich the resulting (*R*)-pantolactone's enantiopurity to 99 %. The high step economy, readily available reactants, cost-effectiveness, no use of hazardous chemicals, low reaction conditions, and ease of use of this process make it superior to conventional techniques.

2.4. Trimethylimidazolidin-4-one hydrochloride catalyst

Several pharmaceutical molecules, including amlodipine, isradipine, dioscorine, and (+)-calanolide, contain 1,4-dihydropyridines and 4*H*-pyran derivatives as significant structural elements (Shehab and Ghoneim, 2016; Nazari et al., 2017). Research on hybrid compounds with combinations of these two heterocyclic functionalities is an intriguing way to make use of the bioactivities of both 1,4-dihydropyridines and 4*H*-pyran moieties. Pham *et al.* synthesized new 1,4-dihydropyridine and 4*H*-pyran hybrid compounds i.e. 4*H*-pyrano[2,3-b]pyridine derivatives **70a-f**. The required products were produced through the activation of an organocatalyst **C9** in the reaction between 1,4-dihydropyridines **68** and acrolein **69**. The reaction begins when acrolein **69** reacts with trimethylimidazolidin-4-one hydrochloride catalyst **C9** to form iminium ion **71** which goes through Michael addition to the 1,4-dihydropyridine **68** to afford cationic adduct **72**. After the enamine's hydrolysis and potential hydrate production, cyclization produces the bicyclic compound **74**, which, upon dehydration, yields the desired 4-hydroxypyrano[2,3-b]pyridine hybrid molecule **70** (Scheme 10) (Pham et al., 2020). When these synthetic products were examined for cytotoxicity against HepG2 and KB cancer cell lines, the results were extremely encouraging: every molecule had an IC_{50} of at least moderate, three compounds (**70a**, **70b**, and **70c**) had $IC_{50} < 10$ mM and one compound **70c** had $IC_{50} < 1$ mM.

2.5. Triphenylphosphine catalyst

One significant class of biologically active heterocycles is composed of oxazinones and oxathiinones (Miyauchi et al., 1996; Piergentili et al., 2007; Singh et al., 2011; Méndez-Rojas et al., 2018). Oxazinones and their benzoid derivatives have a range of medicinal properties, including anticancer (Bolognese et al., 2002), antiviral (Abood et al., 1997; Jarvest et al., 1997), antithrombotic (Hsieh et al., 2005), antimycobacterial (Waisser et al., 2000), anti-inflammatory (Hsieh et al., 2004), antidiabetic, and hypolipidemic (Madhavan et al., 2006) actions. Phosphine-induced organocatalyzed reactions are a potent method for producing heterocycles of sulfur, nitrogen, and oxygen. Gholami *et al.* produced novel benzoxazinones **73** and benzoxathiinones **74** via PPh_3 **C10** catalyzed reaction of aminophenol **71a** or 2-mercaptophenol **71b** with alkyl X-phenylpropiolates **72** (Scheme 11). The process begins as Ph_3P **C10** is added to alkyl X-phenylpropiolate **72** to generate zwitterionic intermediate **75** which is protonated by **71a** and **71b** to yield vinylphosphonium cation **76** and the anionic intermediates **77** and **78**, respectively. Path a involves a nucleophilic substitution reaction between **76** and **77**, forming intermediate **79**, which is then transformed into compound **80** through intramolecular Michael addition. By losing a proton, intermediate **80** produces compound **82**, which is then changed to **84** by removing PPh3 and tautomerization. In path b, **78** undergoes Michael addition to **76** to form ylide **85**, which then experiences 1,2-proton exchange and the loss of PPh_3 to yield the required product **87** (Scheme 12) (Gholami et al., 2019). The antioxidant and antibacterial



Scheme 10. Trimethylimidazolidin-4-one hydrochloride catalyzed synthesis of 1,4-dihydropyridines and 4*H*-pyran derivatives.

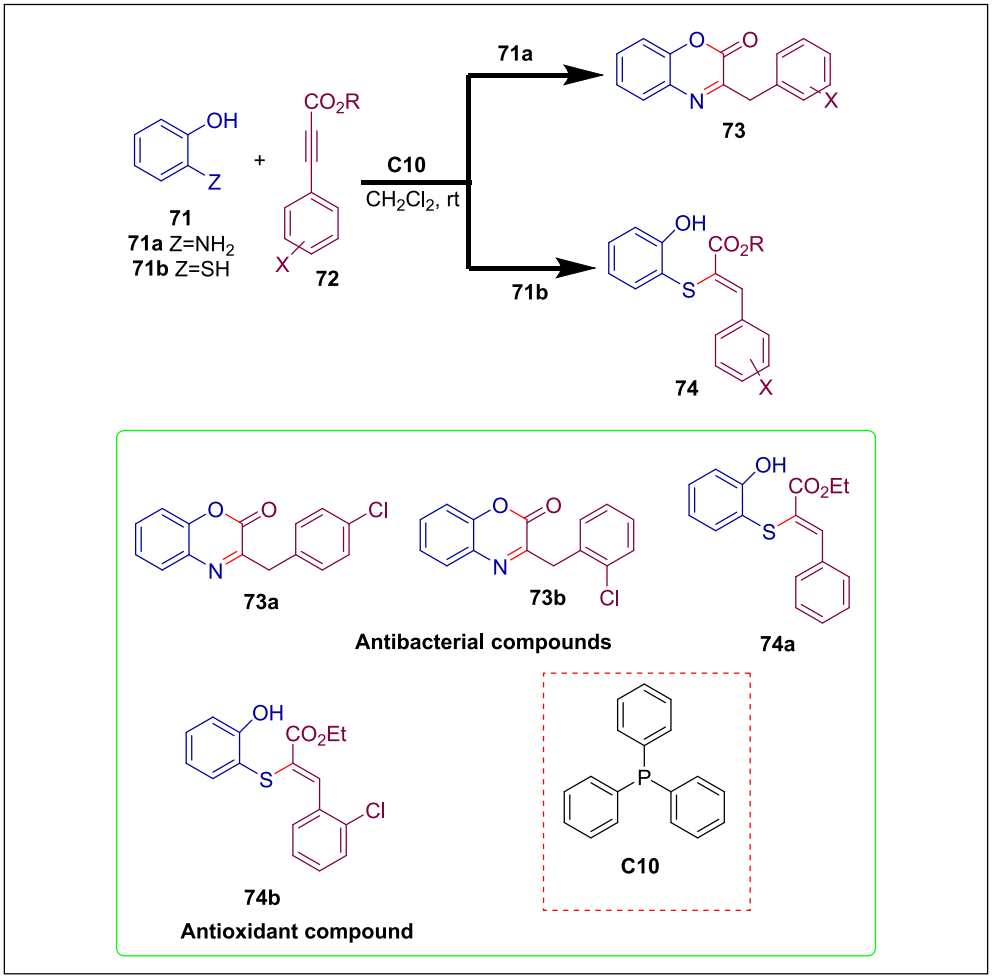
properties of the produced compounds were assessed. Compounds **73a**; **73b** and **74a** possess greater antibacterial activity against *S. aureus*, *B. subtilis*, and *E. coli* bacteria, however, compound **74b** has the most potent antioxidant activity (93.6 %).

Summary

Lewis base organocatalysts are an essential tool in modern synthesis because of their remarkable efficiency in stimulating organic reactions by donating electron pairs to electrophilic substrates. These catalysts, often containing nucleophilic centers such as nitrogen, phosphorus, or oxygen, operate by interacting with electrophiles to increase their reactivity or stabilize transition states. Lewis base catalysts enhance nucleophilicity of the substrate to start the catalytic cycle. The resulting complex undergoes a reaction and then releases the product and the catalyst for further turnover (Fig. 1). Lewis base catalysts' metal-free nature, cost-effectiveness, and potential to minimize waste make them an excellent choice for sustainable and green chemistry. In this section, we have described different Lewis base catalysts such as Hayashi-Jørgensen, *N*-heterocyclic carbene, *tert*-leucinamide, trimethylimidazolidin-4-one hydrochloride, and tri-phenylphosphine catalysts for the synthesis of valuable pharmacophores showing various bioactivities i.e. antibacterial, antidepression, anticancer, anti-oxidizing, and anti topoisomerase I.

3. Lewis acid catalysis

Lewis acids are of particular interest when discussing the synthesis of



Scheme 11. PPh_3 catalyzed synthesis of benzoxazinones and benzoxathiinones.

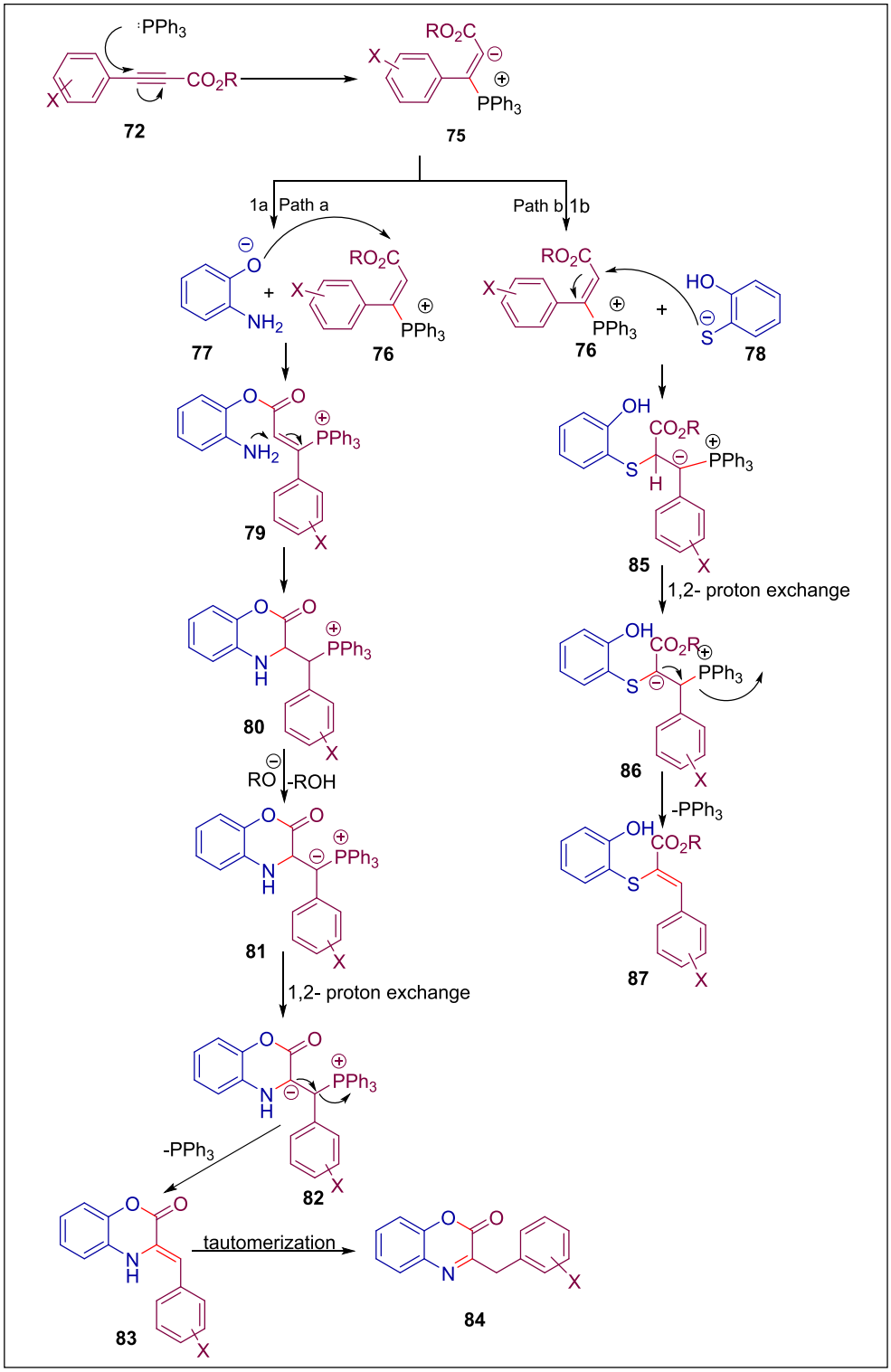
novel chiral organocatalysts since they often stimulate reactions by electrophilically activating organic functional groups (such as carbonyl compounds, imines, and epoxides) toward nucleophilic attack (Schenker et al., 2011). Lewis acid catalysis allows important chemical reactions such as Friedel-Crafts, Diels-Alder, and several aldol, Mannich, and Michael reactions. As a result, extensive research has been done on enantiopure Lewis acids, which has made significant asymmetric modifications of these reactions possible (Hollis et al., 1993). A major drawback of enantioselective Lewis acid catalysis, despite the abundance of sophisticated catalysts and techniques developed in this field, is the necessity for frequently high catalyst loadings. This is due to problems like insufficient Lewis acidity, which prevents some substrate classes from being accessible at all, product inhibition, hydrolytic instability, and competition with nonenantioselective background catalysis (Carreira and Singer, 1994; Hollis and Bosnich, 1995). List et al. synthesized in situ silylated disulfonimide Lewis acid organocatalysts with catalyst loadings as low as 10 parts per million (ppm) (10–15) for highly enantioselective Mukaiyama-type reactions involving silylated nucleophiles (Gatzenmeier et al., 2016). Recently, a new class of catalysts i.e. the C–H acids, which are composed of binaphthyl-allyltetrasulfones has been developed. These catalysts were found to be extraordinarily active Lewis acid catalysts for enantioselective Diels-Alder reactions of cinnamates with cyclopentadiene upon in-situ silylation.

3.1. Trimethylsilyl trifluoromethanesulfonate catalyst

Isoxazolidines have been identified as viable therapeutic candidates because of their intriguing pharmacological characteristics such as antiviral (Loh et al., 2010)and anticancer (Bonanomi et al., 2020).Š tadániová *et al.* reported a novel synthetic method utilizing the organocatalyst trimethylsilyl trifluoromethanesulfonate (TMSOTf) **C11** to produce 1,2,3-triazoles containing the 3-hydroxymethylated 4-hydroxyisoxazolidine moiety **95**. The mechanism of this protocol involves elimination reactions of 5-acetoxyisoxazolidines **88** with a catalytic amount of Trimethylsilyl trifluoromethanesulfonate in the presence of BSTFA in anhydrous *N*-methyl-2-pyrrolidone (NMP) to afford 2,3-dihydroisoxazoles **89** which are treated with of $K_2OsO_4{\cdot}2H_2O$ in the presence of aqueous *N*-methylmorpholine-*N*-oxide (NMO) in CH_3COCH_3/H_2O to yield diastereomeric mixtures of isoxazolidine-4,5-diols **90**, consisting of four inseparable isomers, which are then converted into the corresponding *O*-benzoylated isoxazolidines **91a,b** *via* utilizing DMAP. After reacting with acetonitrile, the isoxolidines **91a,b** form diastereomeric mixtures of azidoisoxazolidines **92a,b**. The synthesized azidoisoxazolidine **92a** is further treated with phenylacetylene to give soxazolidinyl triazole **93** which undergoes debenzoylation to yield isoxazolidin-4-ol **94** which is then desilylated to yield the required 4-hydroxyisoxazolidinyl triazoles **95** (Scheme 13) (Štadániová et al., 2020). The inhibitory action of this produced compound was assessed on the MOLM-13 cell line and found that compound **95** displayed a moderate increase in cell death and suppression of metabolic activity.

3.2. Hyamine catalyst

Quinoline and its derivatives, primarily quinolones, have pharmacological properties (Wen et al., 2015; Gu et al., 2017). Many medicines,



Scheme 12. Mechanism of synthesis of benzoxazinones and benzoxathiinones.

including ciprofloxacin, sparfloxacin, ofloxacin, norfloxacin, and gatifloxacin, are quinoline-based. Numerous attempts have been made to eliminate the negative effects of these drugs and antibiotics. The need to find novel antimicrobials arises from this situation. Arora *et al.* presented a sophisticated hyamine-catalyzed heteroannulation of the quinoline ring with dimedone to synthesize the corresponding azepinone analogues (Scheme 14) (Arora et al., 2018). The procedure entails reacting dimedone **96** with *o*-aminobenzoic acid **97** and isatoic anhydride **98** to produce acridine dione derivatives (**105** and **106** respectively) which are then agitated with $NH_2OH.HCl$ in water and with a hyamine catalyst **C12** to produce the corresponding oximes (**99** or **100**). When a freshly produced organocatalyst is added, these oximes (**99** or **100**) undergo Beckmann rearrangement, yielding the corresponding quinolino-annulated azepinones (**101** or **102**), respectively (Scheme 15) (Arora et al., 2018). This catalyst is prepared by heating cyanuric chloride (TCT) with dimethylformamide. It exhibits excellent catalytic

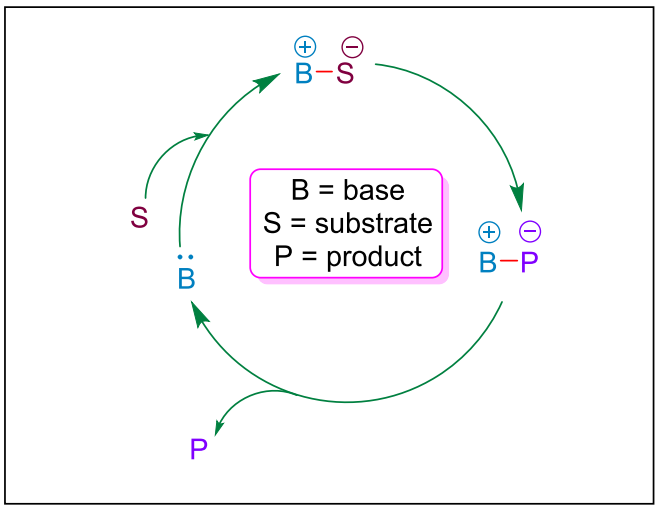
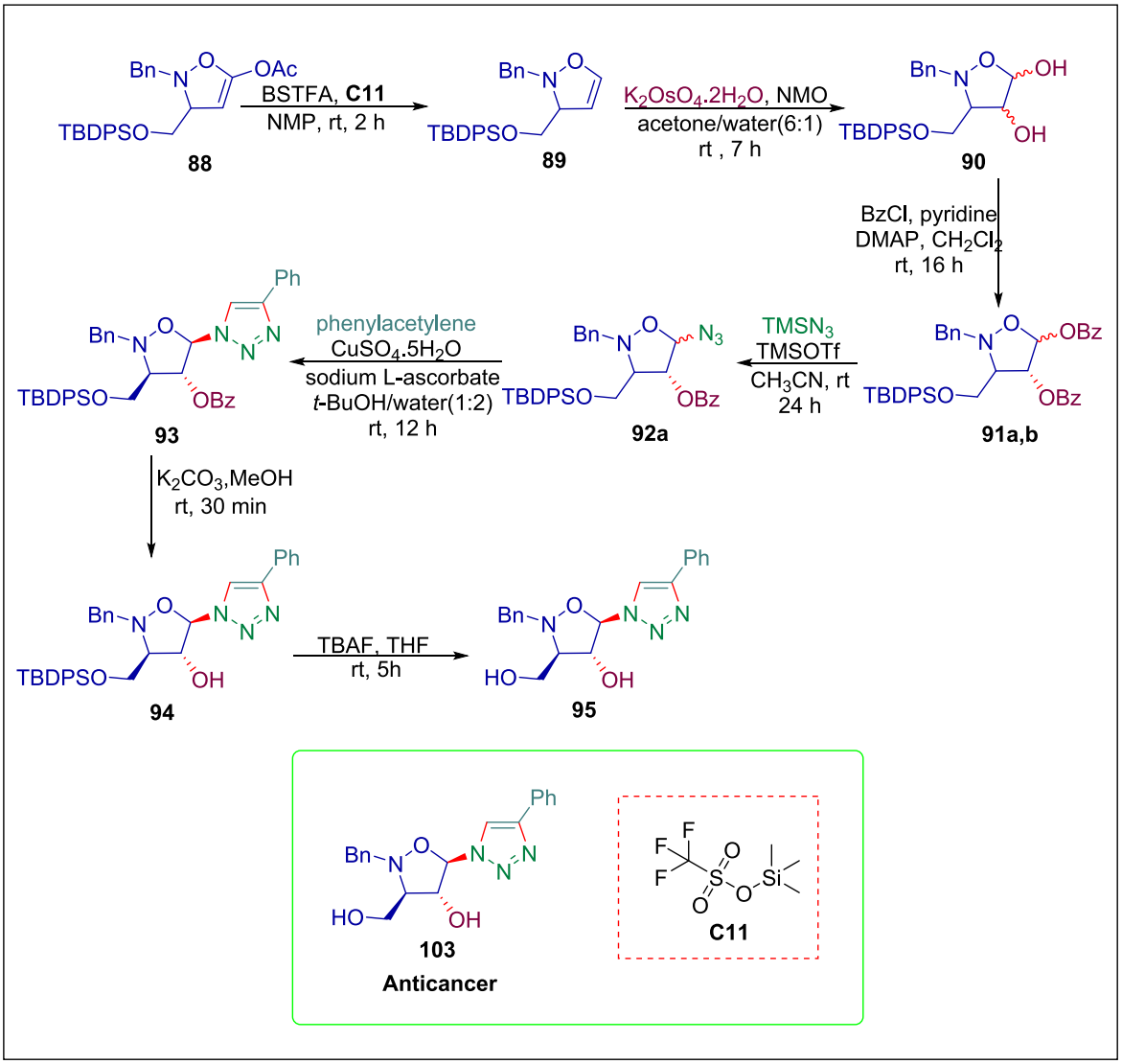


Fig. 1. Mechanism of Lewis base catalysis.

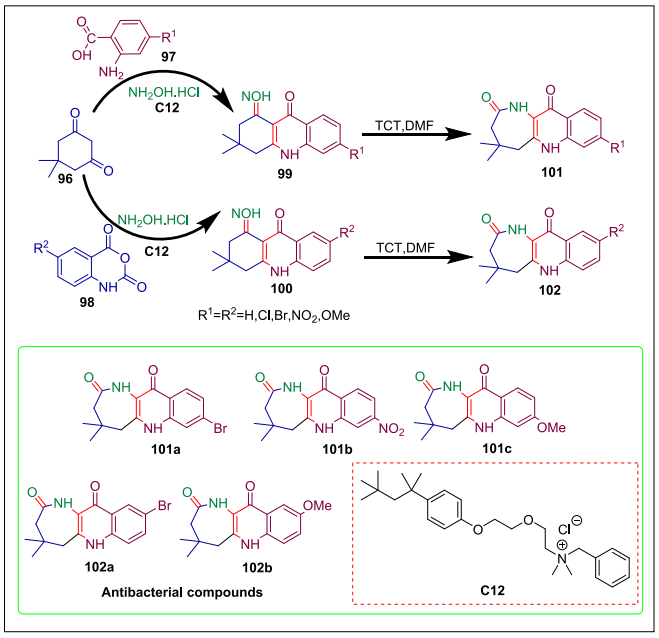
activity, high efficiency, and ease of handling throughout the rearrangement process, which is one of its benefits. These synthetic azepinones were screened against two Gram-positive and two Gram-negative bacteria to assess their antibacterial activity. Compounds **101a** and **102b** demonstrated MICs of 15 μg/mL in the case of *Staphylococcus aureus*, indicating greater potency than the reference antibiotic streptomycin. Comparably, compound **101b**'s MIC of 10 μg/mL for *Bacillus subtilis* showed that it was more effective than the standard drugs tetracycline (30 μg/mL) and streptomycin (40 μg/mL). Significantly lower MIC values (05 and 01 μg/mL, respectively) were observed for compounds **101a** and **102a** compared to tetracycline (25 μg/mL) and reference streptomycin (55 μg/mL). Similarly, compounds **101a** and **102c** had remarkable minimum inhibitory concentrations (MIC) of 10 and 20 μg/mL, respectively, in contrast to reference drugs streptomycin (20 μg/mL) and tetracycline (55 μg/mL).

3.3. Cinchonidine-derive quaternary ammonium catalyst

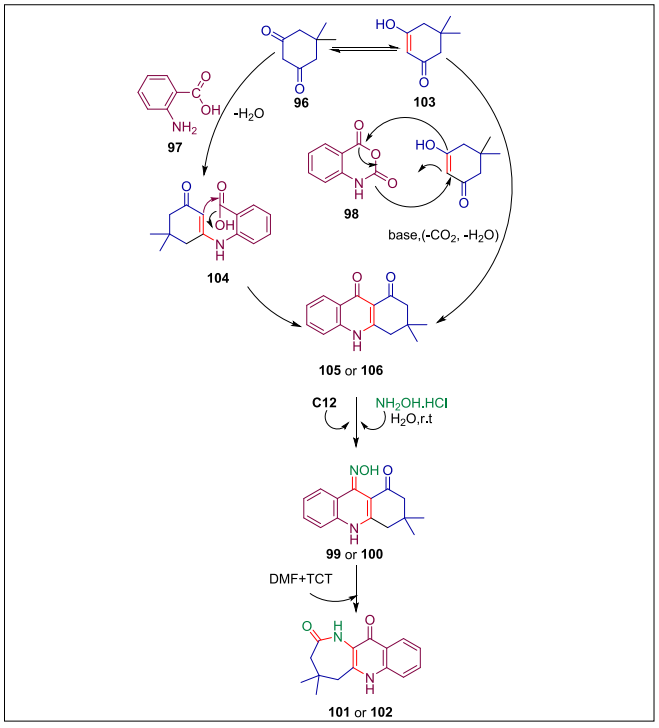
Development of enantiomerically pure compounds is a persistent need in the current chiral pharmaceutical market primarily due to the pure enantiomers' better therapeutic efficacy and safety profile over their racemates. One such example is bicalutamide (Fradet, 2004), a first-generation nonsteroidal androgen receptor (AR) antagonist that is



Scheme 13. Trimethylsilyl trifluoromethanesulfonate catalyzed synthesis of 1,2,3-triazoles bearing the 3-hydroxymethylated 4-hydroxyisoxazolidine moiety.



Scheme 14. Hyamine-catalyzed synthesis of quinolino annulated azepinones.



Scheme 15. Mechanism of synthesis of quinolino-annulated azepinones.

mainly used to treat prostate cancer by selectively blocking the AR. The R isomer of bicalutamide has an almost exclusive antiandrogenic action, which can be explained by the (R)-enantiomer's 30-fold greater binding affinity to AR than the S isomer. Chen *et al.* used cinchonine/cinchonidine-derive quaternary ammonium salt **C13** as a catalyst to develop a method for the asymmetric oxohydroxylation of readily available methyl/ethyl α-benzenesulfonylmethyl-β-aryl enoates and α-bromomethyl-β-aryl enoates with permanganate (Chen et al., 2024).This reaction demonstrated strong enantioselectivities and good tolerance for a broad range of substrates under mild conditions. In just three to five steps, the synthesized enantioenriched α-hydroxy-β-ketone esters (**108a** and **108b**) were successfully used in the diversity-oriented synthesis of 2-arylmethyl-substituted bicalutamide analogue **111**. After undergoing reductive deoxygenation (Lopez and Salazar, 2013), the asymmetric oxohydroxylation products **108a** and **108b** yield the α-hydroxy ethyl esters **109a** and **109b**, respectively. Then through ester hydrolysis and amide production, (*R*)-**111**, a reported (*R*)-bicalutamide analogue (Guerrini et al., 2014), was effectively synthesized (Scheme 16).

3.4. Boron trifluoride diethyl etherate catalyst

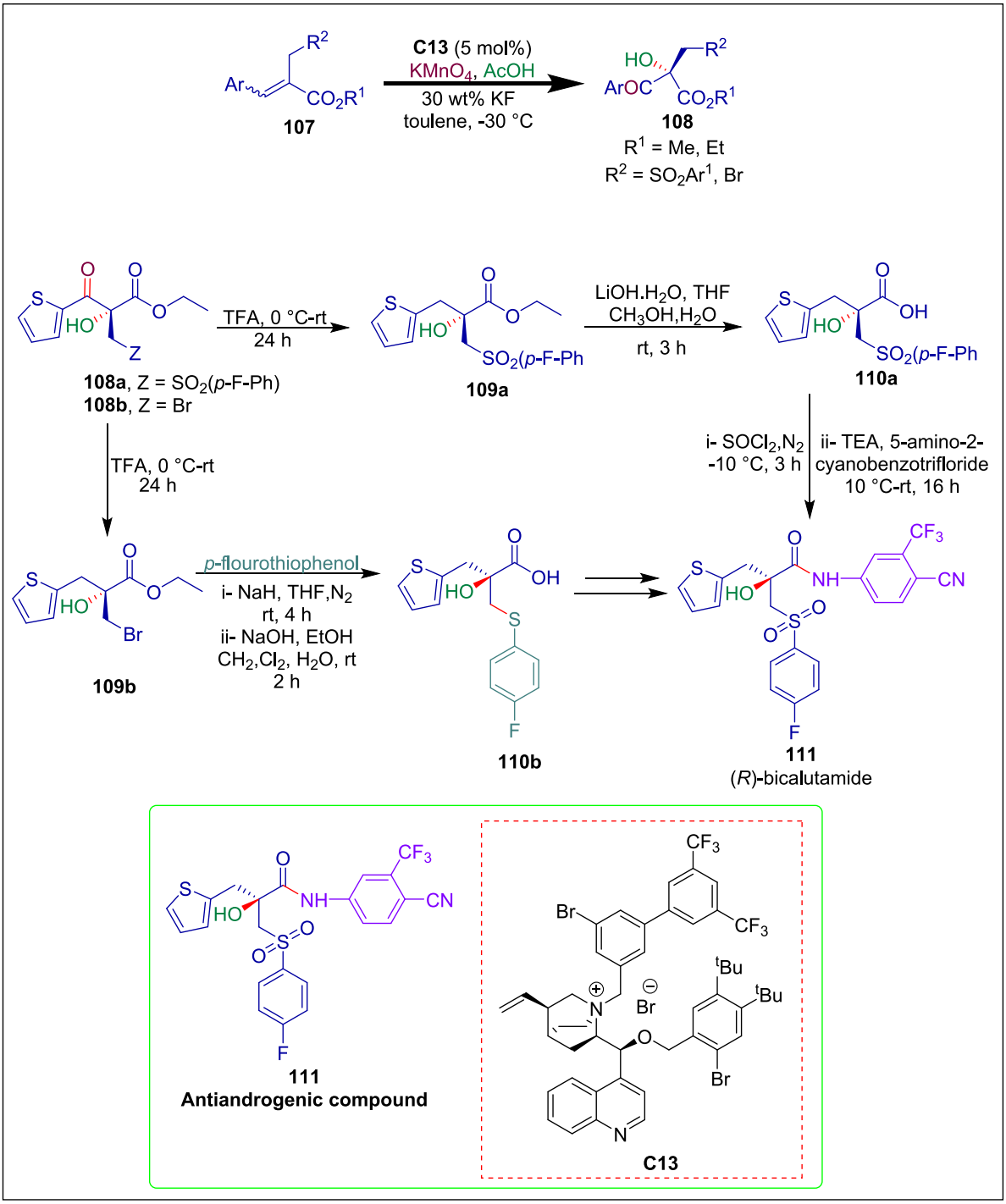
Many natural compounds and active pharmaceutical products, such as naftopidil, naproxen, and suramin (Wang et al., 2012), are made up of fused naphthalenes, which are also actively used as ligands (Bai et al., 2019).So, it is preferable to develop simple synthetic methods for synthesizing functionalized naphthalenes. Mahecha-Mahecha *et al.* reported a simple methodology for the synthesis of functionalized cycloalkane-fused naphthalenes by using Lewis acid catalyst **C14** and readily available substrates. Arylboronic acid pinacol esters **112** undergo Suzuki-Miyaura coupling reaction with cycloalkenyl triflates **113** to form aryl-substituted cyclohexene derivatives **114**which are further cyclized by using boron trifluoride diethyl etherate catalyst **C14** and yield desired fused naphthalenes **115** (Scheme 17) (Mahecha-Mahecha et al., 2020).

3.5. Ethylaluminum dichloride catalyst

Fluorinated compounds are widely found in organic materials, agrochemicals, and pharmaceuticals1 because of their special biophysical characteristics such as lipophilicity (Smart, 2001), metabolic stability, bioavailability. Therefore, the synthetic community has been consistently interested in developing effective and practical methods to access fluorinated compounds. In this regard, *gem*-difluorinated cyclopropanes have become useful fluorine-containing building blocks for organic synthesis. Wu *et al.* reported a Lewis acid-catalyzed cross-coupling reaction between mono- or disubstituted *gem*-difluorinated cyclopropanes **116** and electron-rich arenes and allylsilanes **117** to synthesize fluoroallylic products **120** and fluorinated 1,5-dienes **121**. First, an aluminum complex **122** is formed because of the strong affinity between fluorine of **116** and the Lewis acid $EtAlCl_2$ **C15**, which then undergoes fluoride abstraction to produce the cyclopropyl cation intermediate **123**. The ring tension is then released, causing C–C bond cleavage to generate a more stable fluoroallyl cation intermediate **124**. Ultimately, the nucleophiles **125** attack the electrophilic fluoroallylic cation species **124** to form the C–C bond, which delivers the allylation product **126** and regenerates the Lewis acid catalyst by releasing a molecule of HF (with arene nucleophiles) or TMSF (with allylsilane nucleophiles) as a byproduct (Scheme 18) (Wu et al., 2022). The synthesis of a bioactive-related molecule **120a** with a fluoroalkene moiety further illustrated the practicality of this method.

Summary

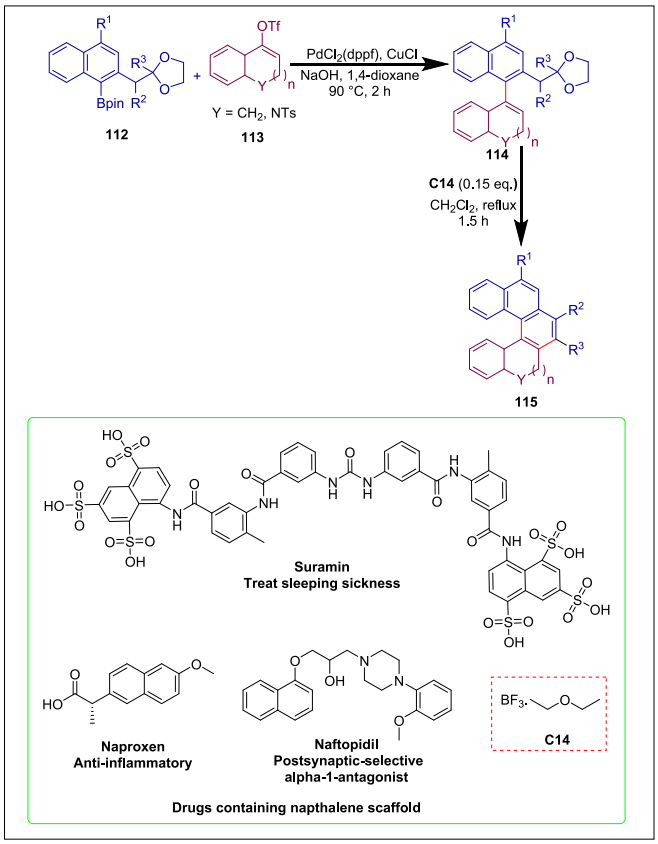
Lewis acid organocatalysts are a class of catalysts that increase the electrophilicity of the reaction intermediates by accepting electron pairs from nucleophilic substrates. Usually composed of atoms like silicon, aluminum, or boron, these catalysts have electron-deficient centers that can coordinate to lone pairs of electrons on nucleophiles. This coordination lowers the energy barrier for the reaction by stabilizing negative charges or activating electrophiles for nucleophilic attack. A common mechanism includes the Lewis acid binding to carbonyl oxygen, increasing the electrophilic nature of the carbonyl carbon, rendering it more susceptible to nucleophilic attack (Fig. 2). These catalysts offer an effective and environmentally friendly substitute for conventional metal-based Lewis acids by enabling reactions to continue at milder conditions with improved selectivity. This section describes the usage of various Lewis acid catalysts e.g. trimethylsilyl trifluoromethanesulfonate and hyamine for synthesizing anticancer and antibacterial compounds.



Scheme 16. Cinchonidine-derive quaternary ammonium catalyzed synthesis of (R)-bicalutamide analogue.

4. Bronsted base catalysis

Chiral organic Bronsted bases have been identified as extremely effective and selective catalysts for enantioselective synthesis. They are frequently employed in asymmetric organic synthesis, and the key factor of the Bronsted base catalysis is the presence of acidic "hydrogen" in the substrates (Zhang et al., 2018a). Common examples of organic Brønsted base catalysis in asymmetric synthesis are hydrocyanation reactions e.g. the Strecker reaction and cyanohydrin synthesis (Seayad and List, 2005). An ongoing problem in the study of Bronsted base catalysis is broadening the range of pronucleophiles that can be used in enantioselective reactions. Typically, chiral *tert*-amines have been frequently used as chiral Brønsted base catalysts (Marcelli and Hiemstra, 2010). P1-phosphazenes, cyclopentenimines, and chiral guanidines are examples of chiral uncharged organobases that have higher basicity than *tert*-amines and have recently become effective chiral Brønsted base catalysts (Uraguchi et al., 2007; Leow and Tan, 2009; Bandar and Lambert, 2012; Nunez et al., 2013). However, the limited basicity of these traditional chiral organobases restricts pronucleophiles to extremely acidic molecules like β-dicarbonyl compounds and nitroalkanes, which limits the feasible chemical conversions that can be catalyzed by chiral Brønsted base catalysis. In 2020 Kondoh *et al.* overcame the intrinsic limitations of pronucleophiles by developing a new chiral Brønsted base catalysts which comprise a P2-phosphazene as an organosuperbase and



Scheme 17. Boron trifluoride diethyl etherate catalyzed synthesis of fused naphthalenes.

a chiral guanidine as a hydrogen bond donor for substrate recognition. Its strong catalytic activity was shown in the less acidic α-phenylthioacetate enantioselective direct Mannich-type reaction (Kondoh et al., 2020).

4.1. Pyrrolidine catalyst

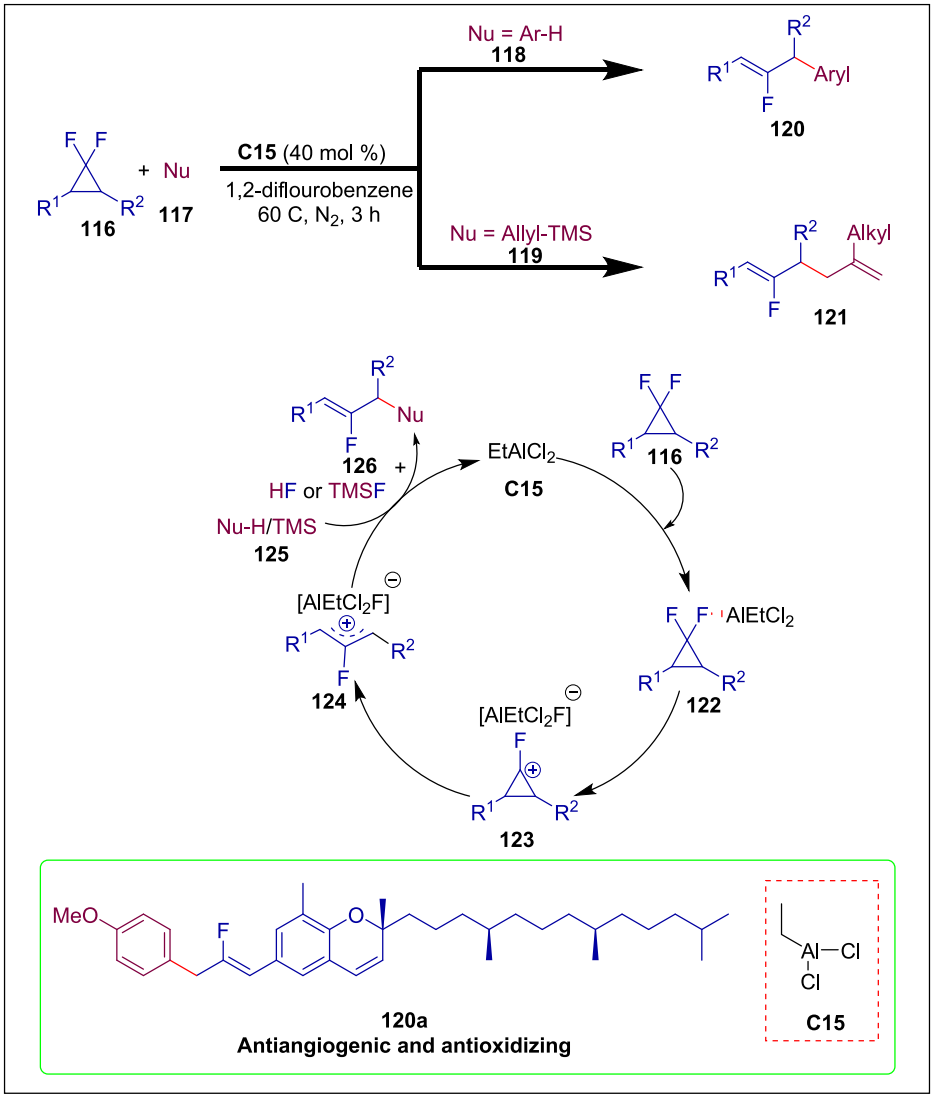
The meroterpenoid applanatumol B is generated by the therapeutic fungus *Ganoderma applanatum*. It has a fused dioxacyclopenta[cd] indene motif and exhibits antirenal fibrosis activity (Luo et al., 2016) Simek *et al.* created a unified organocatalyzed method for synthesizing meroterpenoid applanatumols B. The process begins with 2,5-dihydroxyacetophenone **127** being protected as dibenzyl ether which undergoes an aldol addition with 4-pentenal **128** and subsequent acidic dehydration to give dienone **129**. Afterward, α-aminoxy ketone **131** is produced by a novel tandem reaction comprising nucleophilic allylation/alkoxide-accelerated oxy-Cope rearrangement and radical oxygenation. Then **131** is heated to a 5-*exo*-trig cyclization temperature, yielding an inseparable mixture of cyclopentanes **132a**, **b**, and **c** and trace amounts of 6-endo cyclization product **132d**. The alkoxyamine function in the inseparable crude mixture is removed by oxidative means, resulting in a mixture of aldehydes **133a**, **b**, and **c** which is transformed by Pinnick oxidation, furnishing a separable mixture of carboxylic acids **134a**, **b**, **c** in and cyclohexanone **133d**. Then the esterification of carboxylic acid **133a** and subsequent Johnson-Lemieux cleavage of the terminal olefin yield aldehyde **135** (Yu et al., 2004). The introduction of the remaining carbon atom is achieved by pyrrolidine **C16** catalytic α-hydroxymethylation of **135** leading initially to a 1,3- dioxan-4-ol intermediate which is in situ broken down and reduced to the 1,3-diol unit. Following methyl ester hydrolysis, acid **136** is produced, and it is epimerized to produce tricyclic product **137**. After that, applanatumol B **138** is produced through a small amount of epimerization brought on by the removal of the benzyl-protecting groups (Scheme 19) (Simek et al., 2022).

(−)-Pavidolide B is a natural marine bioactive compound. Tetracyclic diterpenoid (−)-pavidolide B **139** exhibits specific inhibition against the human promyelocytic leukemia cell line HL-60 (IC_{50} = 2.7 μg/mL), according to preliminary biological research conducted on tumor cells (Shen et al., 2012). Zhang *et al.* devised a succinct method for the asymmetric total synthesis of (−)-pavidolide B **139** (Zhang et al., 2017), which was made possible by an intramolecular [3 + 2] annulation reaction of a vinylcyclopropane (VCP) mediated by thiyl radical. 2,4-hexadienal **139** and dimethyl 2-bromomalonate **140** react first in the presence of an organocatalyst (*R*)-2-(diphenyl((trimethylsilyl)oxy) methyl)pyrrolidine **C17** to produce an aldehyde **141**. This aldehyde then goes through hydrolysis and Mitsunobu reaction sequences to form compound **145**, which then goes through the [3 + 2] annulation reaction to produce the desired tricyclic skeletal **146**. Following treatment of this precursor under the circumstances of the Krapcho decarboxylation reaction, aldehydes **147a** and **147b** are produced. Aldehyde **147b** is converted to a homoallylic product *via* Dess-Martin periodinane (DMP) oxidation, which yields diene **149b** which combines with Grubbs II catalyst to produce the tetracyclic skeleton **150b**. Pavidolide B **151** is then obtained by treating **150b** with $RhCl_3{\cdot}3H_2O$ (Scheme 20) (Zhang et al., 2019c). In this strategy, low-cost energy is used to stimulate chemical reactions.

Bridged *N*-heterocycles like morphans and normorphans are significant skeleton of several bioactive compounds (Zhang et al., 2006; Betou et al., 2014). Dixon *et al.* recently synthesized enantioenriched morphans by co-catalyzing the desymmetrization of 4-propargylamino cyclohexanones with chiral amine and chiral silver complexes. Only transition metal catalysts were able to initiate these asymmetric carbocyclization reactions. To create a variety of desirable morphans **153** and normorphans **155** with a broad substrate range and outstanding enantioselectivity (up to 97 % ee), Xu *et al.* developed a metal-free organocatalytic enantioselective desymmetrizing cycloisomerization of arylsulfonyl-protected ynamide-cyclohexanones **152** and **154**. The reaction begins when pyrrolidine catalyst **C18** and the ynamide-tethered cyclohexanone **156** undergo an amine-ketone condensation reaction through intermediate **157** to give the enamine intermediate **158**. The nucleophilic carbon site of **158**′s enamine group can target the α or β position of the ynamide group, resulting in the formation of vinyl anion intermediates **159** or **161** (Marien et al., 2018). The α and β carbons of the Tosyl-containing ynamide are both positively charged because Ts is more electron-withdrawing than Ms. The nucleophilic attack favors the β site to create a sterically less hindered 6-membered ring intermediate **159**, which eventually leads to morphan **160**. Due to the negatively charged β carbon in PG = Ms, the positively charged α carbon site is favored by the nucleophilic addition, forming a sterically more hindered 5-membered ring intermediate, which is the precursor to normorphan **162** (Scheme 21) (Xu et al., 2019b). The greater electron-withdrawing capacity of Tosyl than Mesyl in the ynamide moiety is responsible for the observed protecting-group-dependent regiodivergence. This procedure provides the first amine-catalyzed ynamide reaction, devoid of both Brønsted acid and transition metals, and also the first metal-free asymmetric Conia-ene-type carbocyclization. Furthermore, the bioactivity of the recently synthesized normorphans and morphans as anticancer drugs was examined. Some morphans showed cytotoxic effects on esophageal cancer cells, such as SK-GT-4 and KYSE-450, and nearly half of these morphans demonstrated remarkable cytotoxicity in breast cancer cells, MDA-MB-231 and melanoma cells A375, while the normorphan moieties showed only weak antitumor activity against these five cell lines.

Starting from morphan **163**, the anti-inflammatory drug **165** was also synthesized by reducing the alkenyl and carbonyl groups, oxidizing the CH_2 group next to the nitrogen, and deprotecting the Tosyl group (Scheme 22) (Xu et al., 2019b).

Cathepsin K (CatK) is a key target in the development of treatments



Scheme 18. Ethylaluminum dichloride catalyzed synthesis of flouronated compounds.

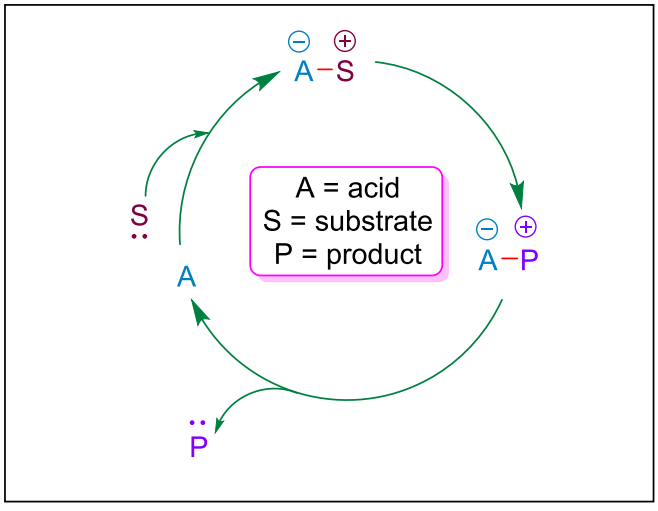
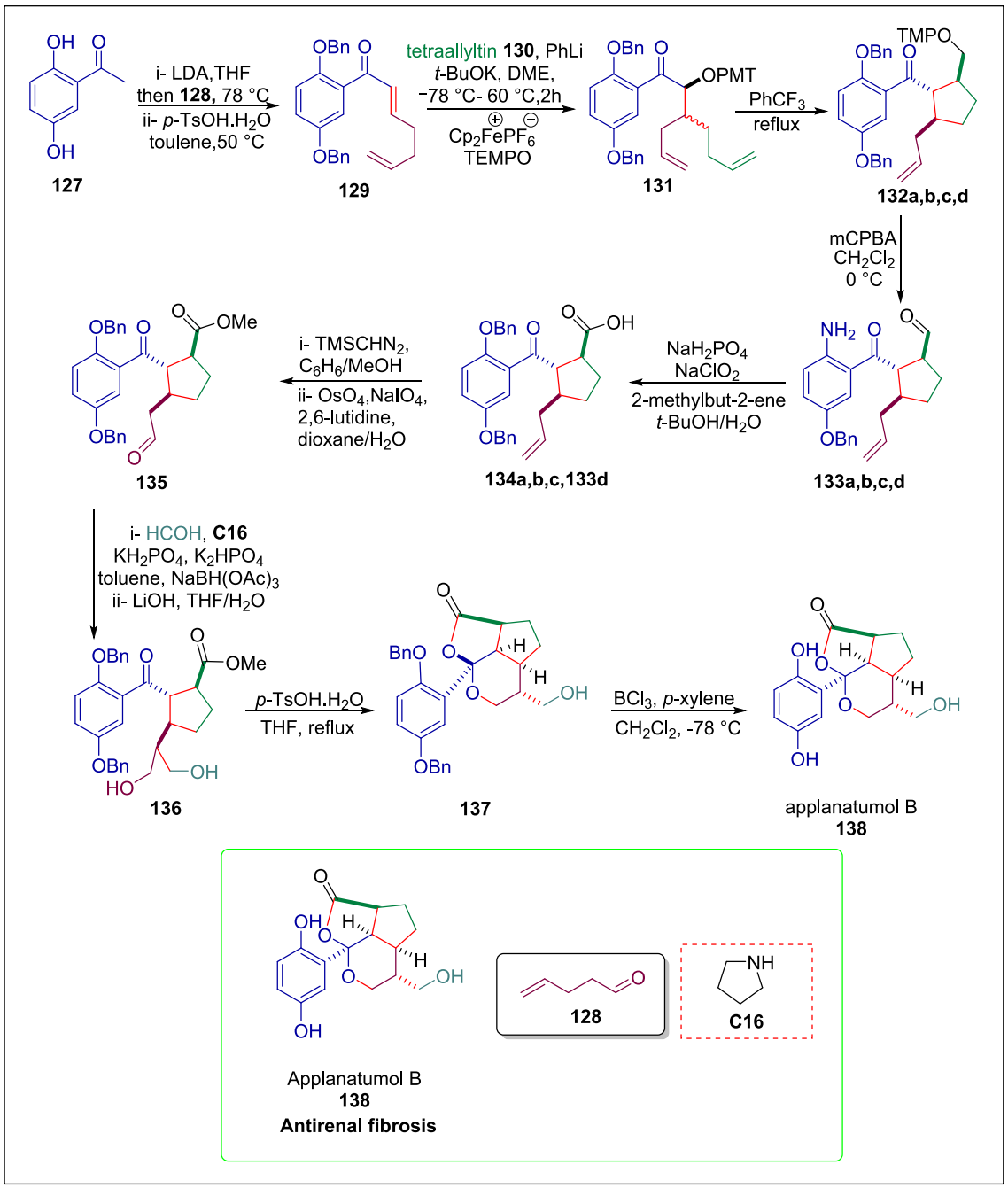


Fig. 2. Mechanism of Lewis acid catalysis.

for bone diseases due to its strong collagenolytic activity (Brömme and Lecaille, 2009; Boonen et al., 2012). It has been reported that epoxypeptidomimetics are strong cathepsin inhibitors. Silva *et al.* described a green synthesis of novel peptidomimetics *via* a one-pot asymmetric epoxidation/Ugi multicomponent reaction. This process permits the use of ethanol/water mixtures as green solvents. These scientists synthesized epoxy-α-acyloxycarboxamides (LSPN690-694) through an asymmetric proline-catalyzed epoxidation ofα,β-unsaturated aldehydes followed by the Passerini multi-component reaction. The reaction begins when α,β-unsaturated aldehyde **166** undergoes proline-derived **C19** catalyzed epoxidation to yield the crude epoxyaldehyde which is then subjected to the Ugi reaction conditions using benzylamine, benzoic acid, and n-butyl isonitrile to give the desired product epoxy-α-acyloxycarboxamides **167** (Scheme 23) (Silva et al., 2020). The synthesized moieties were assessed against CatK and found that the compounds LSPN690 **167a** and LSPN694 **167b** were active with IC_{50} values of 18.45 ± 1.34 μM and 6.44 ± 0.54 μM respectively.

4.2. *1,8-diazabicyclo[5.4.0]undec-7-ene catalyst*

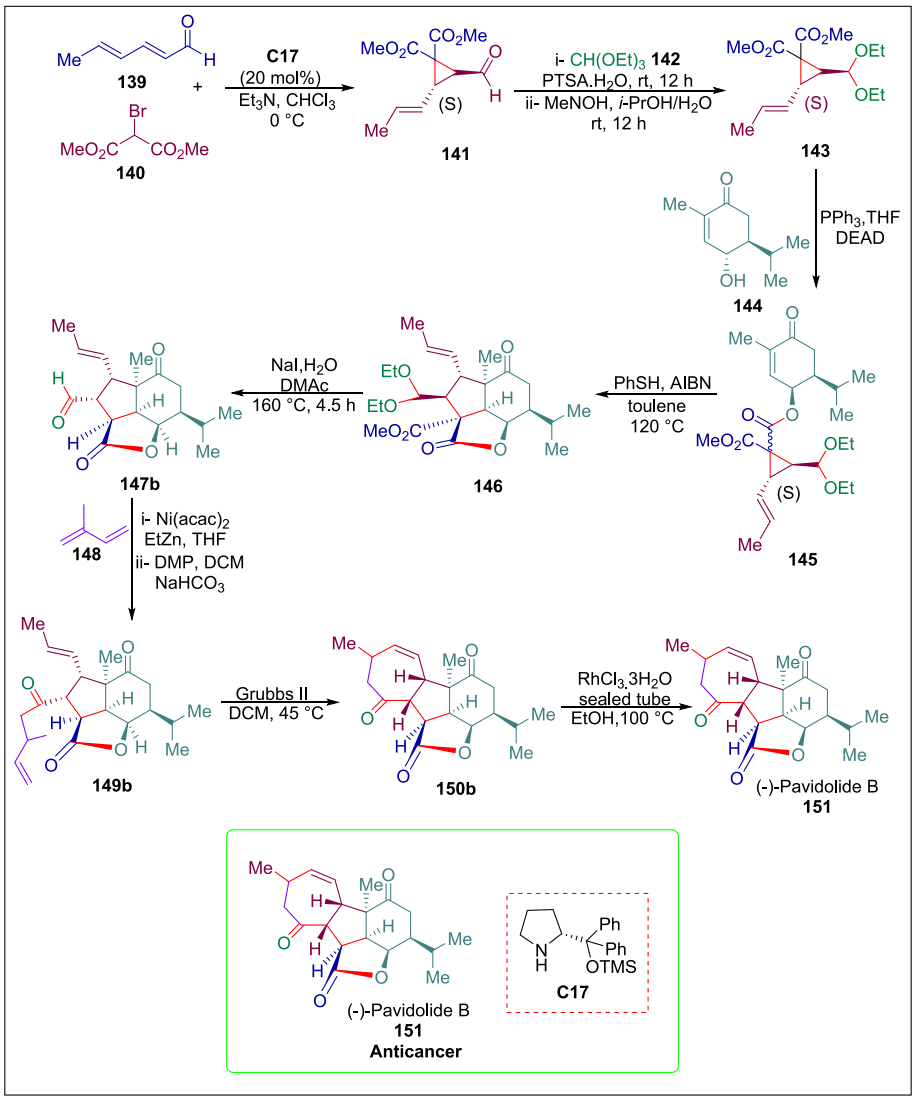
Pyridine derivatives are used as antifungal agents (Enoch et al., 2006). Recently, Zhang et al. used the ester of substituted *α*-amino acid to manufacture tetrahydroimidazo (Dömling, 2002; Zhu and Bienaymé,



Scheme 19. Pyrrolidine catalyzed synthesis of applanatumol B.

2006) pyridine derivatives. Long reaction times (Sun et al., 2010; Hadjebi et al., 2011; Pal et al., 2013a, 2013b, Zhang et al., 2017), the employment of stoichiometric amounts of catalyst (Sun et al., 2010; Zhang et al., 2017), and complicated product isolation processes are some of these methods' drawbacks (Kiruthika and Perumal, 2014; Pal et al., 2014; Zhang et al., 2017; Borah et al., 2023). Musawwer *et al.* created a simple one-pot synthesis of *N*-aryl-1,4-dihydropyridines (1,4-DHPs) by reacting easily obtainable starting ingredients such as malononitrile, aromatic aldehydes, dialkyl acetylenedicarboxylates, and arylamines with organocatalyst DBU **C20**. Initially, dimethyl acetylenedicarboxylate (DMAD) **168**, arylamines **169**, malononitrile **170,** and aromatic aldehydes **171** were reacted under ideal circumstances, yielding products **172**. Compared to electron-donating groups, aromatic aldehydes with electron-withdrawing groups produced better yields in a shorter amount of time. The same process for diethyl acetylenedicarboxylate (DEAD) **173** was next investigated using various aromatic amines **169**, malononitrile **170**, and aromatic aldehydes **171**, resulting in the production of the desired compounds **174** (Scheme 24) (Khan and Saigal, 2018). The current methodology stands out for its good to exceptional yield, fast reaction time, lack of column chromatography required for product purification, and easy experimental setup. The antifungal activity of the products was examined against *Aspergillus niger* (MTCC-281), *Aspergillus fumigates* (MTCC-343), and *Claviceps purpure*. All the products demonstrated moderate to good activity but compounds **160a**, **160b**, **162a**, **162b**, **162c**, and **162d** showed exceptional activity in comparison with the standard drug Nystatin.

The drug zidovudine, also known as 3′-azido-3′-deoxythymidine (AZT), was first created as an antitumoral agent (Ostertag et al., 1974) and now it is also used to treat and prevent AIDS. Zidovudine derivatives exhibit a range of pharmacological characteristics, including antiviral,



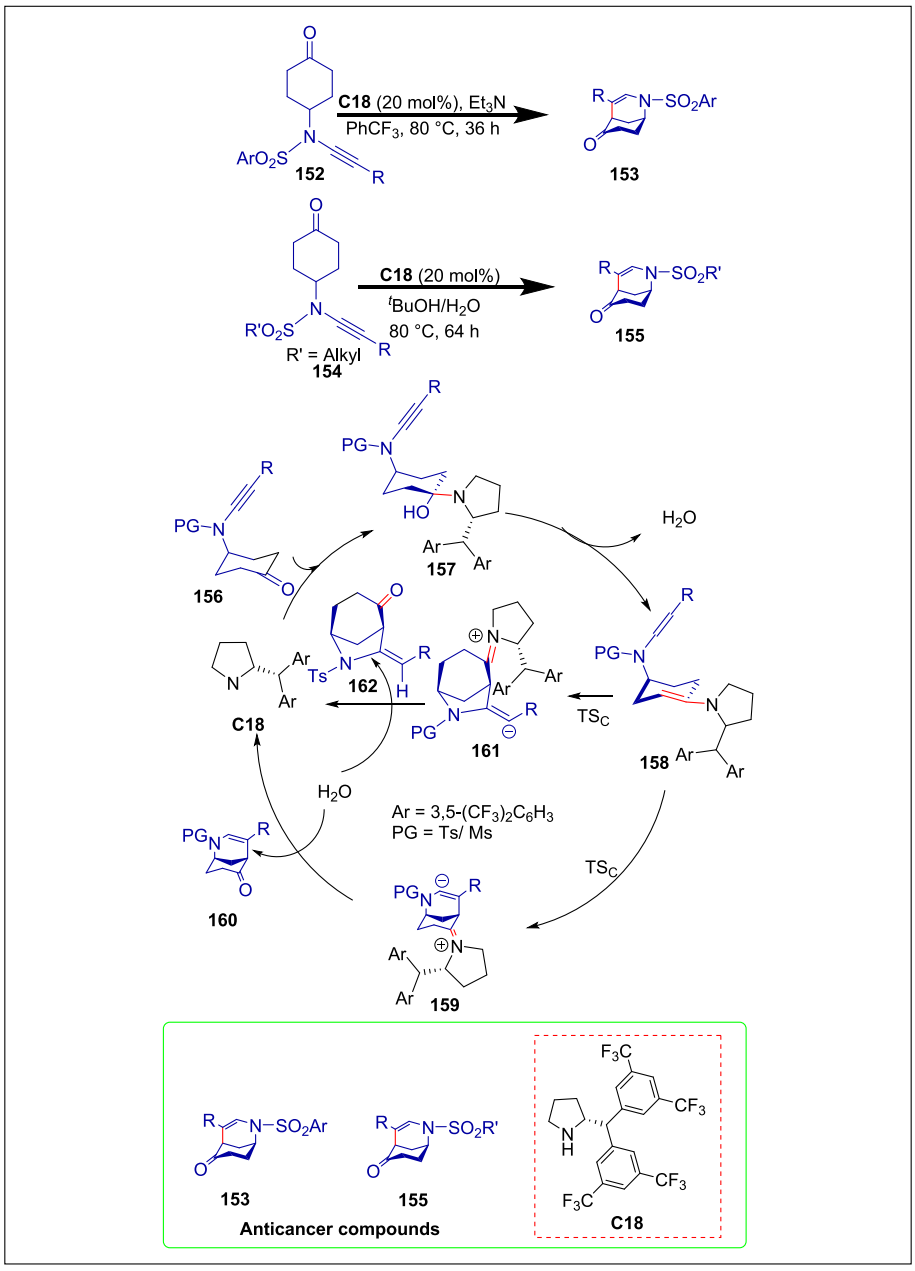
Scheme 20. Pyrrolidine catalyzed synthesis of (−)-pavidolide B.

antioxidant, anticancer, and antibacterial effects (Zhang et al., 2012; de Souza et al., 2015; da Rosa et al., 2017). Gomes *et al.* produced a variety of 1,2,3-triazoyl-zidovudine derivatives **177** using organocatalyzed reactions. By reacting zidovudine **175** with various functionalized keto compounds **176**, such as *β*-keto-amides, *β*-diketones, *β*-keto-esters, *α*-keto-nitriles, and *β*-keto-sulfones, in the presence of DBU **C20**, the hybrid compounds **177** were produced in moderate to good yields (Scheme 25) (Gomes et al., 2020). The afforded products were examined for their antioxidant activity. In mice with equal potency and efficacy, compounds **177a**, **177b, 177c,** and **177d** reduced the production of reactive oxygen species (ROS) and lipid peroxidation in the prefrontal cortex and hippocampal regions. The derivative **177b** demonstrated the best results in the cortex, with an IC_{50} value of 200.80 + 48.55 μM, whereas in the hippocampal region, **177c** was the most potent with an IC_{50} value of 70.95 ± 32.01 μM.

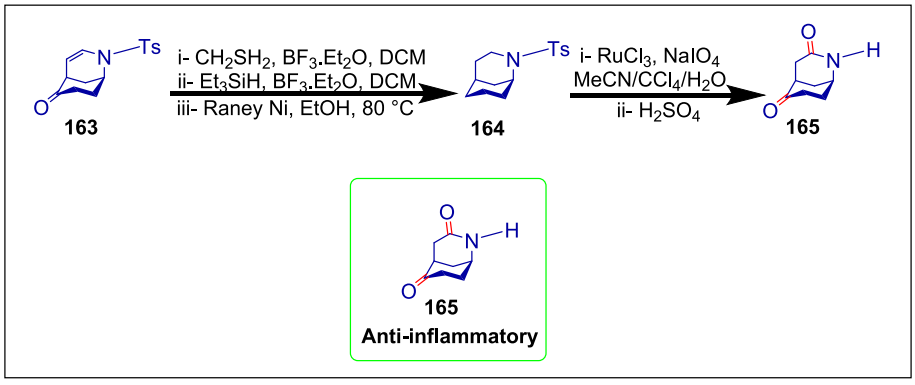
Fluorescent labeling of drugs is a widely used method for investigating their mechanisms of action. The solubility, polarity, and biological activity of the drug under investigation can all be changed by the application of a fluorescent label, which could lead to an inaccurate representation of the mechanism of action under investigation. Therefore, the creation of drugs with built-in fluorescence that can be monitored directly within cells is highly beneficial. Herrmann *et al.* reported a simple process for developing fluorescent hybrid medicines **178**–**185**. This involved combining two easily accessible non-fluorescent pharmacophores with a non-cleavable linker by an organo-click reaction known as azide-carbonyl [3 + 2] cycloaddition, which was catalyzed by Ramachary-Bressy-Wang. The non-fluorescent benzimidazole azide compounds **188**–**192** fuse with non-fluorescent arylacetaldehyde **186** in the presence of a DBU catalyst **C20** to furnish the required fluorescent hybrid drugs **178**–**182**. Following the ester derivative **182**′s deprotection to provide carboxylic acid **193**, the carboxy group of **193** combines with the amine moiety of the readily accessible E3 Ligase ligand **194** to generate the new PROTAC (Proteolysis targeting chimera) **183**. The non-fluorescent benzimidazole azide compounds **188** and **189** undergo DBU-catalyzed fusion to aldehyde **187** to form the required 2-deoxy-artemisinin-benzimidazole hybrid compounds **184** and **185** respectively (Scheme 26) (Herrmann et al., 2023). All freshly obtained fluorescent compounds displayed stronger anti-HCMV activity (EC_{50} down to 0.07 ± 0.00 μM) than the standard drug ganciclovir (EC_{50} = 2.60 ± 0.50 μM) and **179** was the most potent compound with EC_{50} = 0.07 ± 0.00 μM.Scheme 27

4.3. *Cinchona alkaloids-derived catalyst*

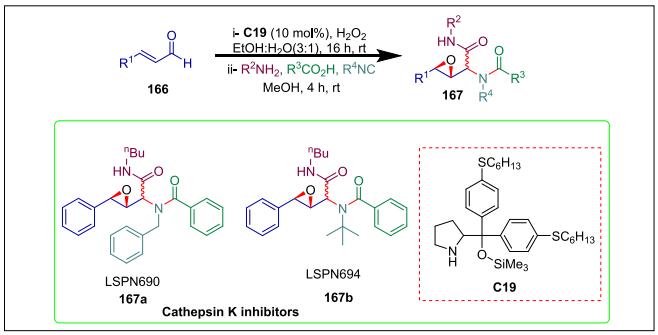
Epoxy ketone moieties are important pharmacophores e.g. cerulenin, a known FabB/F inhibitor (Price et al., 2001). Ernouf *et al.* synthesized *α*;



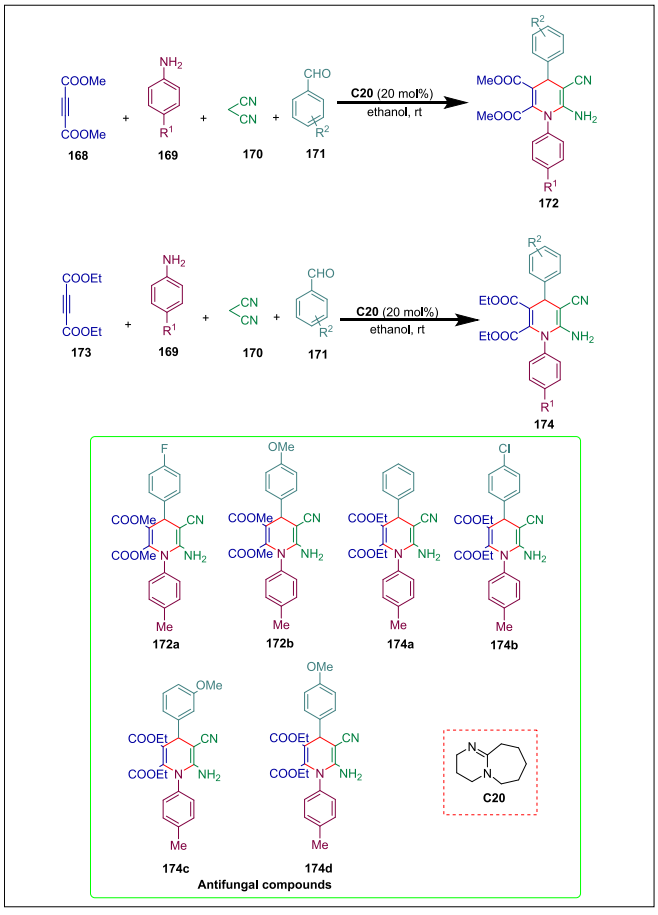
Scheme 21. Pyrrolidine catalyzed synthesis of morphans and normorphans.



Scheme 22. Pyrrolidine catalyzed synthesis of an anti-inflammatory drug.



Scheme 23. Pyrrolidine catalyzed synthesis of epoxy-acyloxycarboxamides.



Scheme 24. DBU catalyzed synthesis of *N*-aryl-1,4-dihydropyridines.

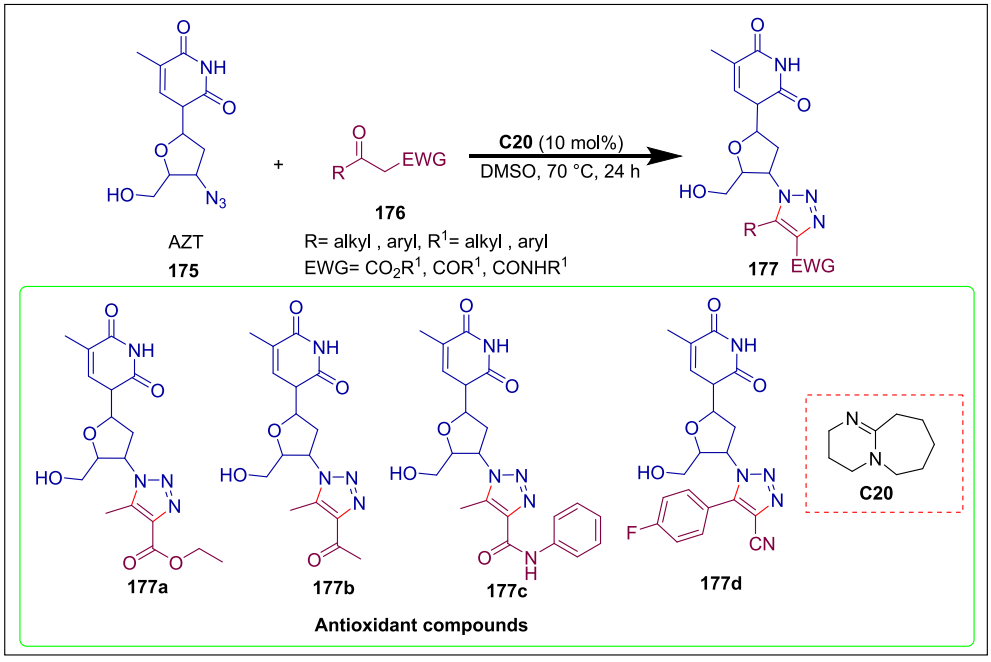
β-unsaturated epoxy ketone *via* organocatalyzed asymmetric epoxidation (Lifchits et al., 2013). The terminal alkene **195** and methyl vinyl ketone (MVK) **196** undergo cross-metathesis to yield the *α*,*β*-unsaturated ketone **197** which undergoes organocatalyzed asymmetric epoxidation in the presence of cinchona primary amine catalysts **C21** and **C22** to produce optically enhanced epoxides **(±)-198**. Following the aldolization of **(±)-198** and acetaldehyde, a diastereoisomeric mixture of alcohols is produced. Methanesulfonyl chloride is then added to the mixture to yield the enone **(±)-199** (Scheme 28) (Ernouf et al., 2018). This *α*; *β*-unsaturated epoxy ketone **(±)-199** was investigated for antibacterial activity and found active against hospital-acquired methicillin-resistant *S. aureus* (HA-MRSA) and community-acquired methicillin-resistant *S. aureus* (CA-MRSA) albeit with IC_{50} values of 43 μg/mL and 32 μg/mL.

In pharmaceutical chemistry, *α*-carbolines are intriguing structural motifs (Debnath et al., 2021). They are extensively present in several natural products and exhibit a variety of biological properties, for example cytotoxic (Moquin-Pattey and Guyot, 1989; Lin et al., 2016), antibacterial, and antifungal properties (Saundane et al., 2013). It has also been demonstrated that C3-modified spiro-oxindoles are very effective antitumor agents (Fan et al., 2017; Boddy and Bull, 2021). He *et al.* provided the first deprotected organocatalytic asymmetric [3 + 3] annulations of isatin-derived Morita-Baylis-Hillman (MBH) carbonates **200** and indolin-2-imines **201** to create a range of multifunctionalized *α*-carboline-spiro-oxindole hybrids **202** in good to excellent yields with high stereoselectivities. The chiral organocatalyst (quinidine) **C23** is added to the MBH carbonate of isatin **200** to initiate the reaction, resulting in the electrophilic onium salt **203**. Subsequently, the tertiary-butoxide anionic base generated in situ takes a CH_2 proton from **201** to give the carbanion intermediate **204**, which attacks the *γ*-position of the nitrogen ylide **206** through an SN2′ pathway, leading to the allylic adduct **207** once the **C23** is eliminated. Next, in the presence of a base, intermediate **207** is changed into intermediate **208**, which then goes through an intramolecular aza-Michael reaction to produce the required spiro-oxindole *α*-carboline **202** (Scheme 29) (He et al., 2022). Certain afforded compounds suppressed the proliferation of colorectal cancer cells. It was discovered that the most effective compound, **202**, activated autophagy, induced the creation of autophagosomes, and activated the overall autophagy flux in HCT116 cells.

N-substituted 2-pyridones and their derivatives are commonly present in pharmaceutical compounds and physiologically active natural products, such as human rhinovirus protease inhibitors, CG400549 (*anti-Staphlococcus*), and glucokinase inhibitors (Schiebel et al., 2014; Ramirez et al., 2017; Jia et al., 2017; Liu et al., 2017). Several metal-catalyzed reactions have been used in the past to synthesize *N*-substituted 2-pyridones; however, organocatalyzed Michael addition has not been documented (Zhang et al., 2015; Huang et al., 2017; Xu et al., 2019a). Wu *et al.* first time described the synthesis of *N*-substituted 2-pyridones **211** by enantioselective, organocatalytic aza-Michael additions of halogenated 2-hydroxypyridines (pyridin-2(1*H*)-ones) **209** to α,β-unsaturated-1,4-diketones or 1,4-ketoesters **210**. The reaction begins when **212** and **213** undergo cinchonine-derived squaramide **C24** catalyzed Michael addition to give Michael adduct **214** which is reduced via the Baeyer-Villiger reaction to phenyl ester **215**. This ester is then hydrolyzed and reduced selectively to alcohol **216** (Kenner and Seely, 1972; Frein et al., 2009), whose hydroxyl group is then brominated and reduced to get **217** (Hutchins et al., 1977) whose bromo-substituent is transformed to the NH_2 and then isoxazole-3-carboxamido-group (Messaoudi et al., 2010) to prepare desired compound **218** (Scheme 30) (Wu et al., 2019). The reaction conditions are moderate and simple to carry out. High enantioselectivities and good yields were obtained from the Michael adducts. The synthesis of important intermediate **218** (Dragovich et al., 2003; Martinez et al., 2004), for the production of human rhinovirus (HRV) protease inhibitors demonstrated the synthetic application of this approach.

4.4. 1,4-diazabicyclo[2.2. 2]octane catalyst

Alzheimer's is a neurodegenerative disease. An extracellular plaque of amyloid-beta (A*β*) forming in the brain is one of the disease's clinical features. Since BACE1 is essential for the synthesis of A*β*, it has been actively pursued in the search for novel treatments for Alzheimer's disease (Koh et al., 1990; Haass and Selkoe, 2007; Masters and Selkoe, 2012; Vassar et al., 2014; Grujičić and Nikolić, 2021). Winneroski *et al.* previously reported the fragment-based discovery of LY2811376, the first BACE1 inhibitor known to have a significant decrease in human CSF A*β* (May et al., 2011; May et al., 2015). Currently, this group has reported the synthesis of a variety of BACE1 inhibitors through organocatalyzed reactions by using *trans*-cyclopropyl scaffolds as structural constraints. The reaction starts when 1,3-dichloroacetone **219** is desymmetrized to phosphorane **220**, and the leftover chloride is



Scheme 25. DBU catalyzed synthesis of zidovudine derivatives.

subsequently replaced with the protected allylamine anion to yield *β*-ketophosphorane **221**, which undergoes Wittig olefination to give *α*-amino enone **222**. Next, enone **222** is cyclopropanated by an organocatalyst DABCO **C25**, yielding the racemic *trans*-cyclopropyl intermediate **223**, which is then subjected to intramolecular [3 + 2] nitrone cycloaddition using $Ti(OEt)_4$ and 4-methoxybenzyl hydroxylamine, resulting in a racemic mixture favoring diastereomer **224**. This diastereomer then undergoes reductive ring opening to yield **225**, which is then processed through two steps to give protected aminothiazine **226** that undergoes subsequent SNAr reaction with 2-chloropyrimine to form **227**. The CH_3MgBr double-addition to the ester group of **227** results in *tert*-alcohol **228** (Scheme 31) (Winneroski et al., 2019). This is then followed by the removal of the protecting group and an acid-catalyzed etherification using (1*R*,2*R*-2-methylcyclopropyl] methanol to yield ether **229**. Compound **229** showed a 40 % decrease in cortical Ab 1-X in PDAPP mice having a dose of 100 mg/kg.

Cyclopropane frameworks are significant structural building blocks found in various natural products and bioactive moieties (Sandanayaka et al., 2003; Brackmann and de Meijere, 2007; Tripathi et al., 2017). Previously cyclopropane building blocks were synthesized through metal carbenoids to electron-rich or electron-neutral alkenes and Michael-intiated cyclization of alkyl halides (Lee et al., 2012; Rueping et al., 2012) or ylides (Kakei et al., 2007) with electron-deficient alkenes. Chen and He presented the first method to synthesize spirocyclopropyl oxindoles *via* triethylenediamine –catalyzed Michael/alkylation cascade reaction (Xie et al., 2007) of *N*-unprotected 3-bromooxindoles (Zheng et al., 2015a) with *α*,*β*-unsaturated acyl phosphonates involving *α*-substituted ammonium ylide intermediates. 3-bromooxindole **230** reacts with *β*,*β*-disubstituted acyl phosphonates **231** (Esteban et al., 2018) in the presence of DABCO catalyst **C25** to form spirocyclopropyl oxindole **232** (Scheme 32) (Chen and He, 2020). One of these synthesized compounds, compound **232a** is a diastereomer of HIV-1 NNRTI inhibitor **233**.

4.5. 4-pyrrolidinopyridine catalyst

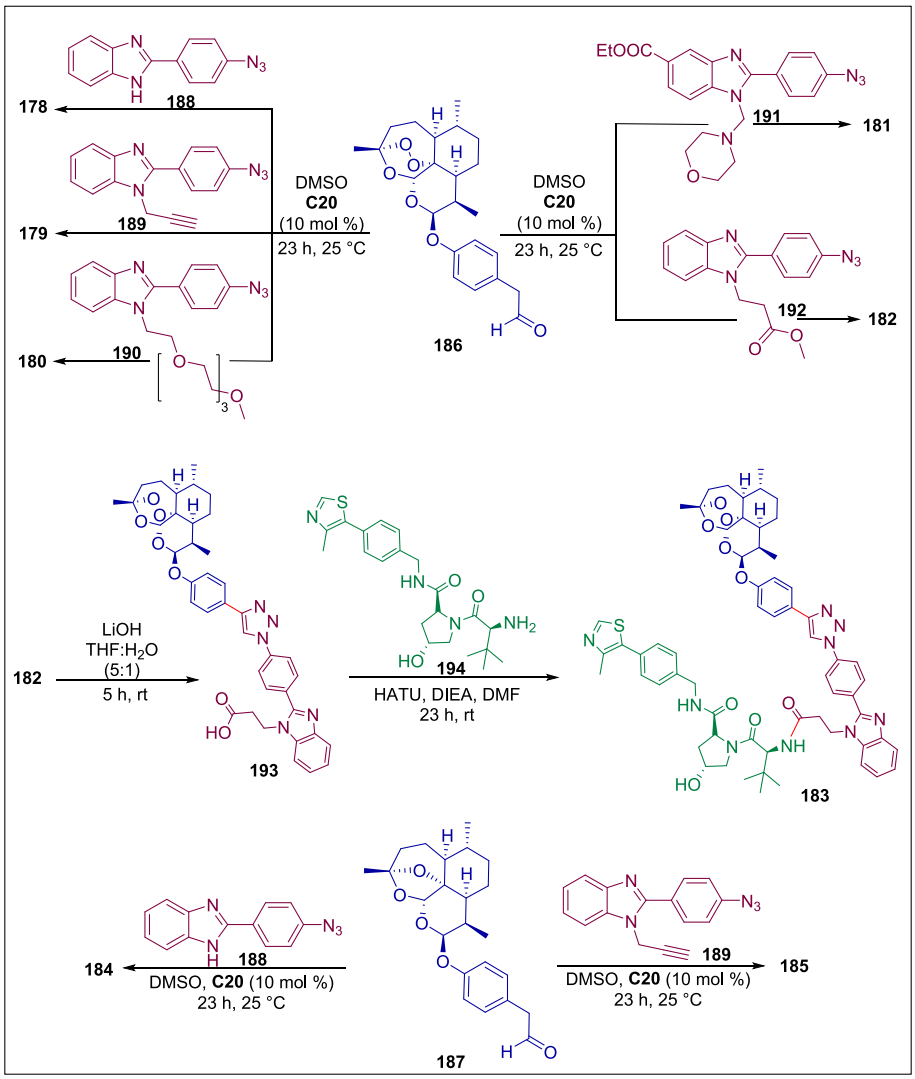
The World Health Organization has recognized *E. coli* as one of the "critical priority" antibiotic resistance bacteria (Tacconelli, 2017). The development of anti-*E. coli* vaccinations is getting a lot of attention due to their resistance to antibiotics. The *O*-antigen is a significant part of the lipopolysaccharide, and a desirable antigen for vaccine development (Micoli et al., 2019; Li and Li, 2020; Seeberger, 2021). A novel one-pot organo-catalysis relay glycosylation method was created by Wan *et al.* to synthesize the dithiolated *O*-antigen of *E. coli* serogroup 64. 3,6-di-*O*-acetyl-2-nitroglucal **234**, trisaccharide glycosyl thiol **235**, and mannosyl acceptor **236** are the three essential components needed for the synthesis. In the presence of the organocatalyst 4-pyrrolidinopyridine (PPY) **C26**, trisaccharide thiol **235** (Tacconelli, 2017) reacts with **234** to produce the tetrasaccharide intermediate. This intermediate is then attached with the **236** to yield the required pentasaccharide **237**, which is then converted into pentasaccharide **238** by removing the bulky TIPS groups and converting the NO_2 group into the corresponding acetamide. Following that, compound **238**′s methyl ester and all benzoyl groups are eliminated to yield compound **239**, which is the dithiolated *O*-antigen of *E. coli* serogroup 64 (Scheme 33) (Wan et al., 2023). This procedure is compatible with a broad range of substrates, mild reaction conditions, moderate to outstanding yields, and high site- and stereoselectivity.

4.6. Triazabicyclodecene catalyst

Near-infrared dyes can act as photosensitizers in cancer photodynamic therapy and help monitor nanocarriers (Pais-Silva et al., 2017). It is necessary to develop modern synthetic techniques to ensure that the drug delivery system's loading and dye photophysical characteristics stay stable for reliable monitoring in biological systems. Oliveira *et al.* disclosed a simple chemical conjugation of the carbocyanine heptamethine near-infrared dye IR780 to polylactide to create a polymeric near-infrared probe (IR-PLA) which allows stable fluorescent tagging of biodegradable polyester nanocarriers. D,L-lactide **240** undergoes Triazabicyclodecene (TBD) **C27** organocatalyzed ring-opening polymerization with a cyclooctyne initiator **241** to afford "clickable" polylactide **242**. Then IR780 **243** is derivatized and conjugated to polylactide **242** through a copper-free one-pot azide-alkyne cycloaddition reaction to furnish IR-PLA **245** (Scheme 34) (de Oliveira et al., 2019).

Summary

A type of catalyst known as Bronsted base organocatalysts works by picking up protons (H^+) from substrates and converting them into nucleophilic entities that can take part in further chemical



Scheme 26. DBU catalyzed synthesis of fluorescent hybrid drugs.

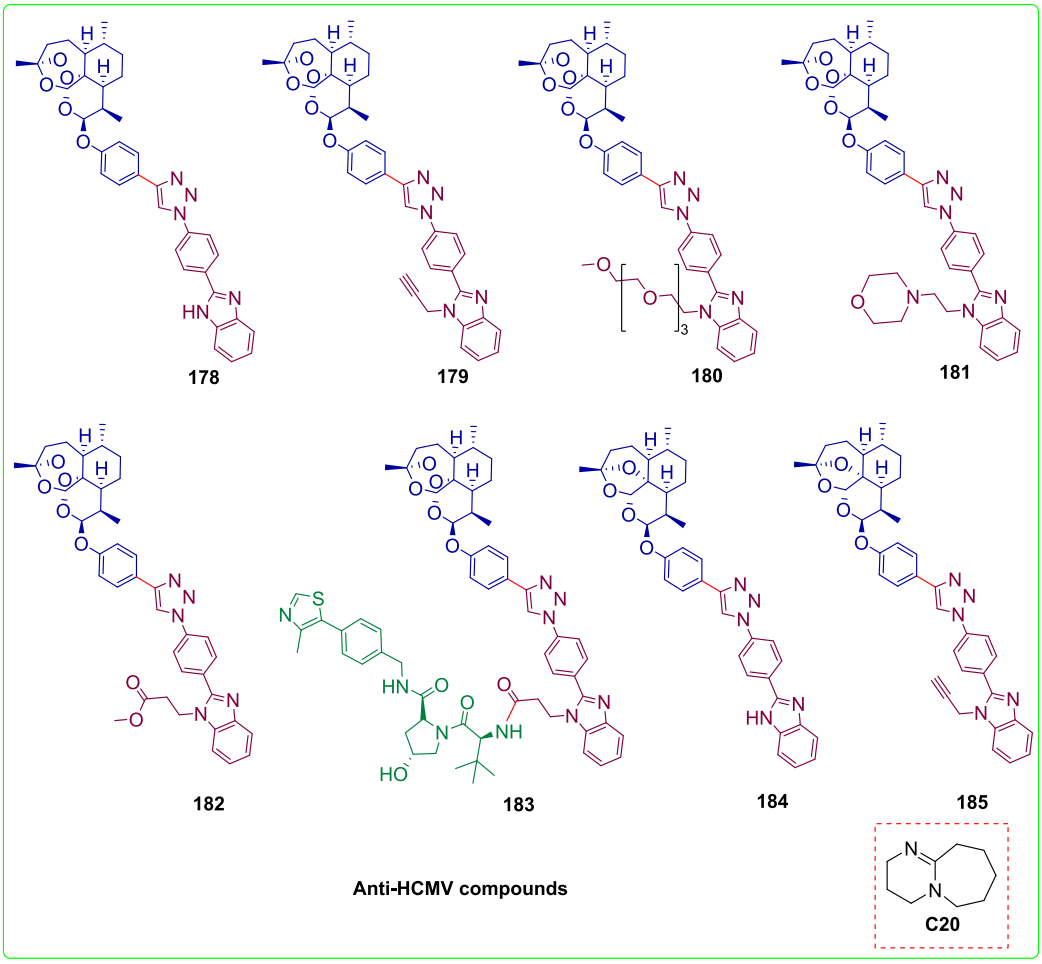
transformations. Usually, these organocatalysts have simple functional groups that serve as proton acceptors, like amidines or amines. One common method includes the deprotonation of acidic protons, such as those in α-carbonyl compounds, leading to the production of reactive enolate intermediates. After that, these enolates can undergo nucleophilic attack on electrophiles, promoting reactions like Michael additions or aldol condensations. The regeneration of the Bronsted base usually marks the end of the catalytic cycle and permits repetition of the procedure (Fig. 3). These catalysts operate under mild conditions, offer high selectivity, and avoid the use of metal-based systems, making them attractive for environmentally benign and sustainable synthetic applications. This section covers the synthesis of remarkable therapeutic agents like applanatumol B, cathepsin inhibitors, human rhinovirus (HRV) protease inhibitors, BACE1 inhibitors, HIV-1 NNRTI inhibitors, dithiolated *O*-antigen of *E. coli*, cytotoxic, anti-inflammatory, antifungal, anti-HCMV, antioxidizing, and antibacterial compounds by using different organocatalysts such as pyrrolidine, 1,8-diazabicyclo[5.4.0] undec-7-ene, 1,4-diazabicyclo[2.2. 2]octane, 4-pyrrolidinopyridine, triazabicyclodecene, and cinchona alkaloid-derived catalysts.

5. Bronsted acid catalysis

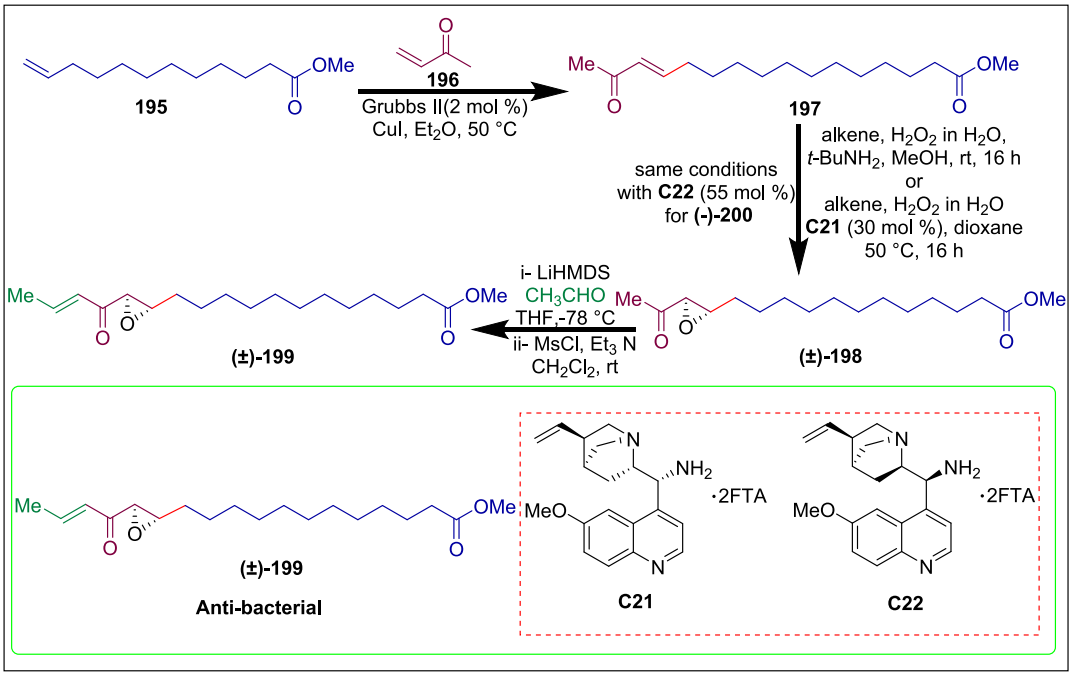
Brønsted acid catalysts increase the reactivity of electrophilic species by lowering their electron density. The exceptional versatility of enantioselective Brønsted acid catalysis stems from the incredibly tiny and labile nature of the catalytic particle, which is an acidic hydrogen atom (Merad et al., 2018). They have mostly been used as catalysts for C-O bond formation and breakage, including hydrolysis and the synthesis of esters and acetals. In the twentieth century, the catalytic activity of Brønsted acids in carbon–carbon bond formation was underestimated. However, Brønsted acids have become effective catalysts for the synthesis of C–C bonds at the start of the twenty-first century. Brønsted acids catalyze the formation of iminium salt, oxonium salt, carbocation, and vinylic carbocation by activating carbonyl, imine, alkene, alkyne, and OH groups, all of which promote the nucleophilic addition (Akiyama and Mori, 2015). In 2020, Lu *et al.* found that azoalkenes could function as carbon–carbon-nitrogen 1,3-dipole surrogates rather than four-atom synthons in asymmetric [3 + 2] cycloaddition reactions with 3-vinylindoles in the presence of chiral phosphoric acid. This resulted in the production of enantioenriched 2,3-dihydropyrroles in high yields and good stereoselectivities (Mei et al., 2020).

5.1. Thiourea catalyst

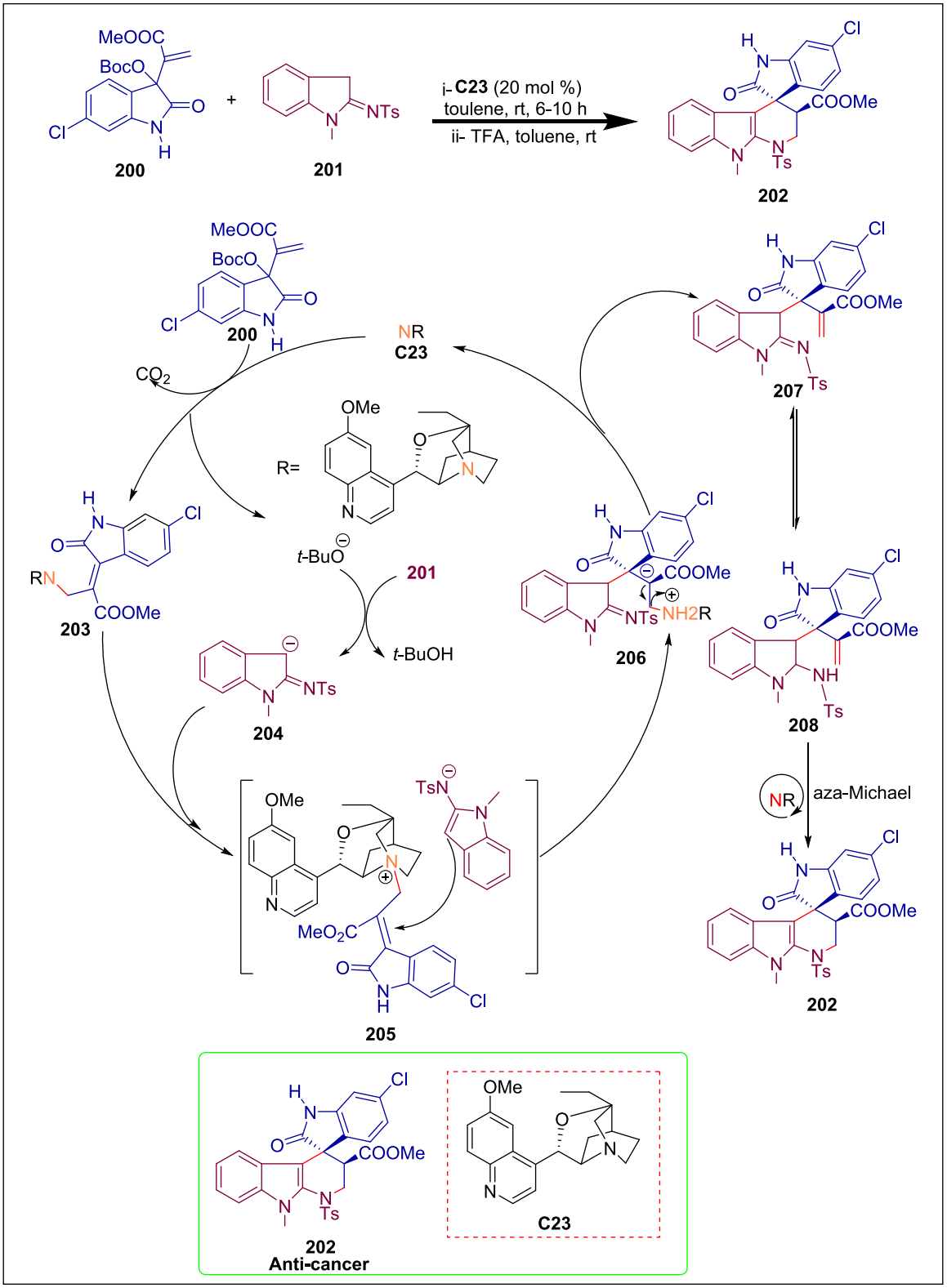
Asymmetric organocatalytic aza-Michael addition of a ketimine with an ortho hydroxyl group (Esteban et al., 2018) to nitroalkenes under batch and flow conditions gives 1,2-diamines. Diamines are significant components for the production of bioactive precursors. It has not yet



Scheme 27. Structures of fluorescent hybrid drugs.

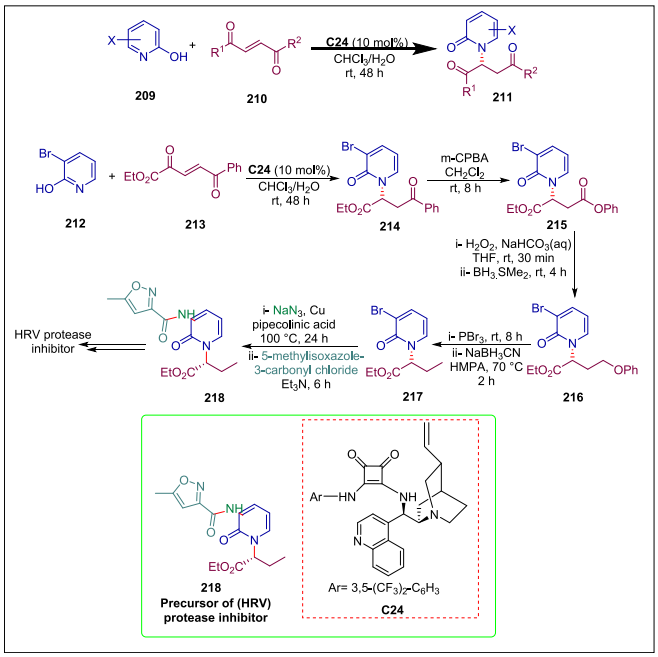


Scheme 28. Cinchona primary amine catalyzed synthesis of α,β-unsaturated epoxy ketones.



Scheme 29. Quinidine catalyzed synthesis of α −carboline-spiro-oxindole hybrids.

been reported how these diamine derivatives were synthesized organocatalytically under flow circumstances. Corella *et al.* carried out a Takemoto's thiourea **C28** catalyzed reaction between *trans*-2,4-dichloro-β-nitrostyrene **249** and a ketimine **246** in batch and flow to obtain compound **250**. Following an hour of residence, **250** undergoes an addition reaction before being exposed to HCl for acidic hydrolysis, which yields the corresponding amine hydrochloride **251**, which is directly protected as a Boc carbamate **253**. After that, its nitro group is reduced to produce amine **254**, which is the intermediate for the synthesis of VNI **255** that has been described in the literature. This procedure, which uses acetone as a green solvent, also recovers the catalyst **C28** in 85 % and the precursor to a ketimine i.e. 2-



Scheme 30. Cinchonine-derived squaramide-catalyzed synthesis of HRV protease inhibitor.

hydroxybenzophenone **246**, in 90 % (Scheme 35) (Guerrero-Corella et al., 2021). The synthesis of VNI, the drug-like equivalent of posaconazole for the treatment of Chagas disease, illustrates the efficacy of this process.

Oxazole compounds exhibit various bioactivities e.g. antifungal (Tomi et al., 2015; Zhang et al., 2017), antibacterial (Škedelj et al., 2013; Patil et al., 2016), anti-inflammatory (Otrubova et al., 2014; Perrone et al., 2015), antiviral (Kim et al., 2013; Zhong et al., 2013), antituberculosis (Meissner et al., 2013; Abhale et al., 2017), anti-cancer (Lu and Wu, 2013; Maini et al., 2015), antiparasiticda Rosa et al. (da Rosa et al., 2017; Taha et al., 2017), and anti-diabetic (Yoon et al., 2014; Kalwat et al., 2016). They are also prone to attach to different enzymes and receptors of the biological systems. Wang *et al.* used an organocatalyst to produce derivatives of oxazol-5-one that contain chiral trifluoromethyl and isoxazole scaffolds through molecular hybridization. *Tert*-leucine **256** reacts with trifluoroacetic anhydride **257** to form *N*-trifluoroalkyl acetylated *tert*-leucine **258**, which then cyclizes to yield intermediate **259**. Next, **259** and 4-nitro-5-styrylisoxazole **260** undergo quinine-derived thiourea **C29** catalyzed Michael addition to yield the desired compounds **261** (Scheme 36) (Wang et al., 2023). The antiproliferative properties of these produced compounds were tested against A549, HepG2, MCF-7, HeLa, and 5637 cancer cell lines. Compound **261a** demonstrated significant anti-cancer activity ($IC_{50} = 1.8 \pm 0.1$ μM) against HepG2 cells and suppressed the growth of cells.

Spirooxindoles and pyran are vital heterocyclic compounds found in many natural products and have displayed a wide spectrum of bioactivities (Nazhand et al., 2020; Zhang et al., 2021a). Prior research by Jin and colleagues revealed the effective NHC-catalyzed [2 + 4] cycloaddition protocol that produced spirooxindole-pyrano[2,3-c]pyrazole compounds with antibiotic properties (Yang et al., 2022). Li *et al.* presented a new and advanced organocatalyzed protocol for the synthesis of spirooxindole containing a tricyclic pyran-annulated benzopyran skeleton. A thiourea-catalyzed **C30** domino reaction between isatylidene malononitrile **262** and 1-(2-hydroxyphenyl)-butane-1,3-dione **263** results in multicyclic spirooxindole products **264** with an *O*,*O*-acetal-fused tricyclic motif or tetrahydroxanthone (Scheme 37) (Li et al., 2023). The obtained compounds show encouraging anticancer activity with low IC_{50} values. The most active compounds are **264a** and **264b**, which have IC_{50} values of 16.47 μM and 17.92 μM, respectively.

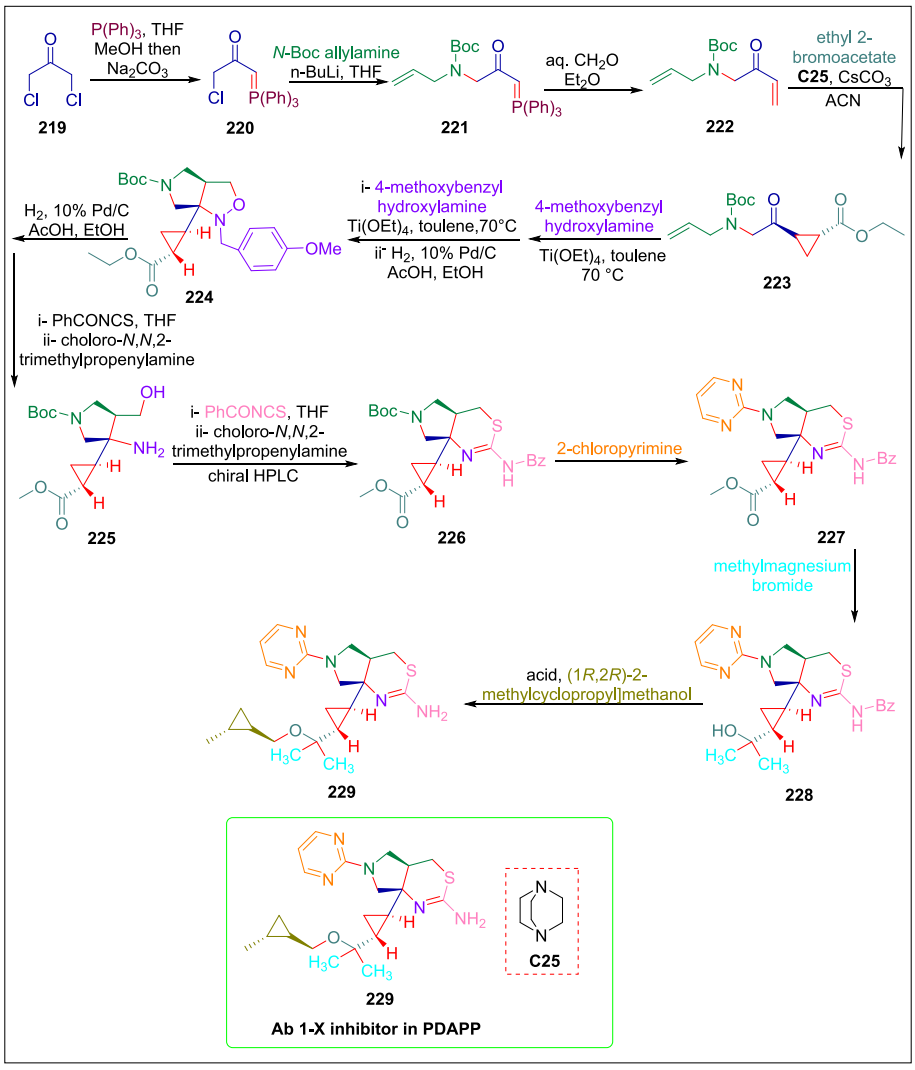
5.2. Chiral phosphoric acid catalyst

Triarylmethanes show remarkable biological activities, such as the ability to inhibit histidine protein kinases and have antiviral, antifungal, antioxidant, and anticancer effects (Ameen and Snape, 2013; Mondal et al., 2018). A key problem in asymmetric catalysis is the successful discriminating between two (typically) sterically identical aryl groups, which is necessary for the production of such large molecules (Besset et al., 2013). Yan *et al.* tackled this problem by implementing an efficient organocatalytic technique that produced effective enantioselection between aryl and heteroaryl groups. Racemic tertiary alcohol **265** undergoes asymmetric reduction with benzothiazoline **266** as the hydride source to form indole-containing triarylmethane **267**. The reaction starts with phosphoric acid-catalyzed **C31** dehydration to form cation **268**, paired with a counter anion. This pair of ions may be in pseudo-resonance, or equilibrium, with the activated indole imine methide form **269**. The hydride source then moves near the benzylic carbon to yield the required molecule **267** (Scheme 38) (Yan et al., 2022). The reaction occurs in mild circumstances with great efficiency and enantiocontrol, which are key aspects of this method. The antiviral and cytotoxic properties of the obtained products were examined. It was found that compound **267a** had a significant antiviral action with an IC_{50} value of 2.27 μM while compound **267b** exhibited high cytotoxicity, with 50 % cytotoxic concentration (CC_{50}) values ranging from 5.6 to 18.2 μM.

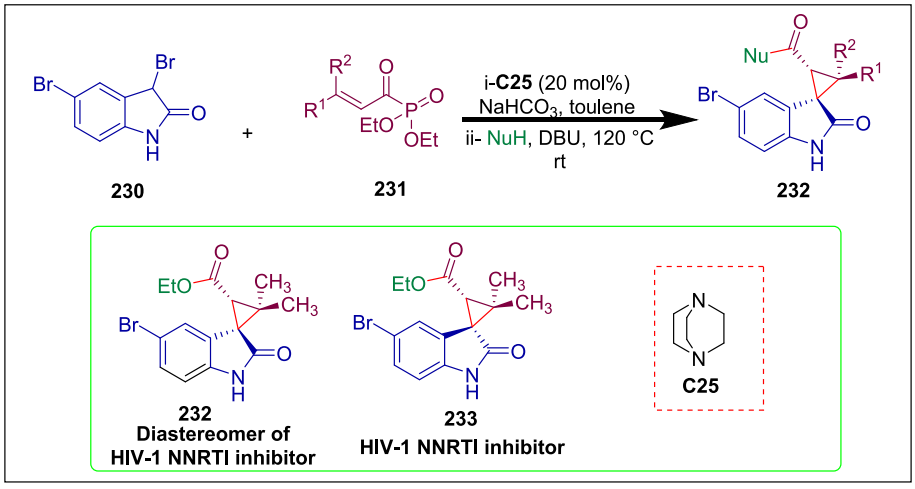
Axially chiral allene scaffolds are commonly found in natural products (Hoffmann-Röder and Krause, 2004; Pu et al., 2009; Cai et al., 2011; Rivera-Fuentes and Diederich, 2012). In the past, Li's group used thiazolones as appropriate nucleophiles in CPA-catalyzed 1,8-addition processes with alkynyl *para*-quinone methides (*p*-QMs) or alkynyl aza-*p*-QMs to create axially chiral tetrasubstituted allenes (Zhang et al., 2019a, b). For the formation of axially chiral allene scaffolds, finding suitable nucleophiles under Brønsted acid catalysis is a crucial problem (Kwon et al., 2018). In the presence, Wang *et al.* developed a chiral phosphoric acid (CPA) *R*-**C32** catalyzed asymmetric construction of hexahydropyrrolo[2,3-b]indole-containing tetrasubstituted allene scaffolds bearing both axial chirality and central through a cascade 1,8-addition/dearomatization-cyclization reaction of *para*-aminophenyl propargylic alcohols **270** with tryptamines nucleophiles **271**. This reaction resulted in various such tetrasubstituted allenes **272** bearing multiple chiral elements in good yields with high diastereo- and enantioselectivities. The reaction starts as *para*-aminophenyl propargylic alcohol **270** is dehydrated leading to the synthesis of alkynyl aza-*para*-QM intermediate **274**. Then, by creating two hydrogen bonds, (*R*)–**C32** activates tryptamine **271** and intermediate **274**. This promotes an enantioselective 1,8-addition/CADA(catalytic asymmetric dearomatization) reaction between the two, resulting in the production of tetrasubstituted allene intermediate **275**, which then goes through a stereoselective intramolecular cyclization process to yield the desired tetrasubstituted allene **272** (Scheme 39) (Wang et al., 2022). A cytotoxicity analysis of these produced products suggested that they can partially suppress the proliferation of pancreatic cancer cells and **272a** is the most potent compound with an IC_{50} value of 86.6(μM).

5.3. α-angelica lactone catalyst

Phthalide-derived scaffolds exist in many pharmaceutical and natural product compounds e.g. 3-butylphthalide, mycophenolate, and fumarate (Napolitano, 1997; Karmakar et al., 2014; Saikia and Gogoi, 2018). Recently, arbutin has been used as a pre-oxidant in the presence of Cu-salt and oxygen gas to create phthalide dervatives by an oxidation process mediated by visible light. The arbutin used in this method is toxic (Finney et al., 2018). Thatikonda *et al.* reported the synthesis of bioactive racemic 3-butylphthalide **277** in 35 % yield by benzylic

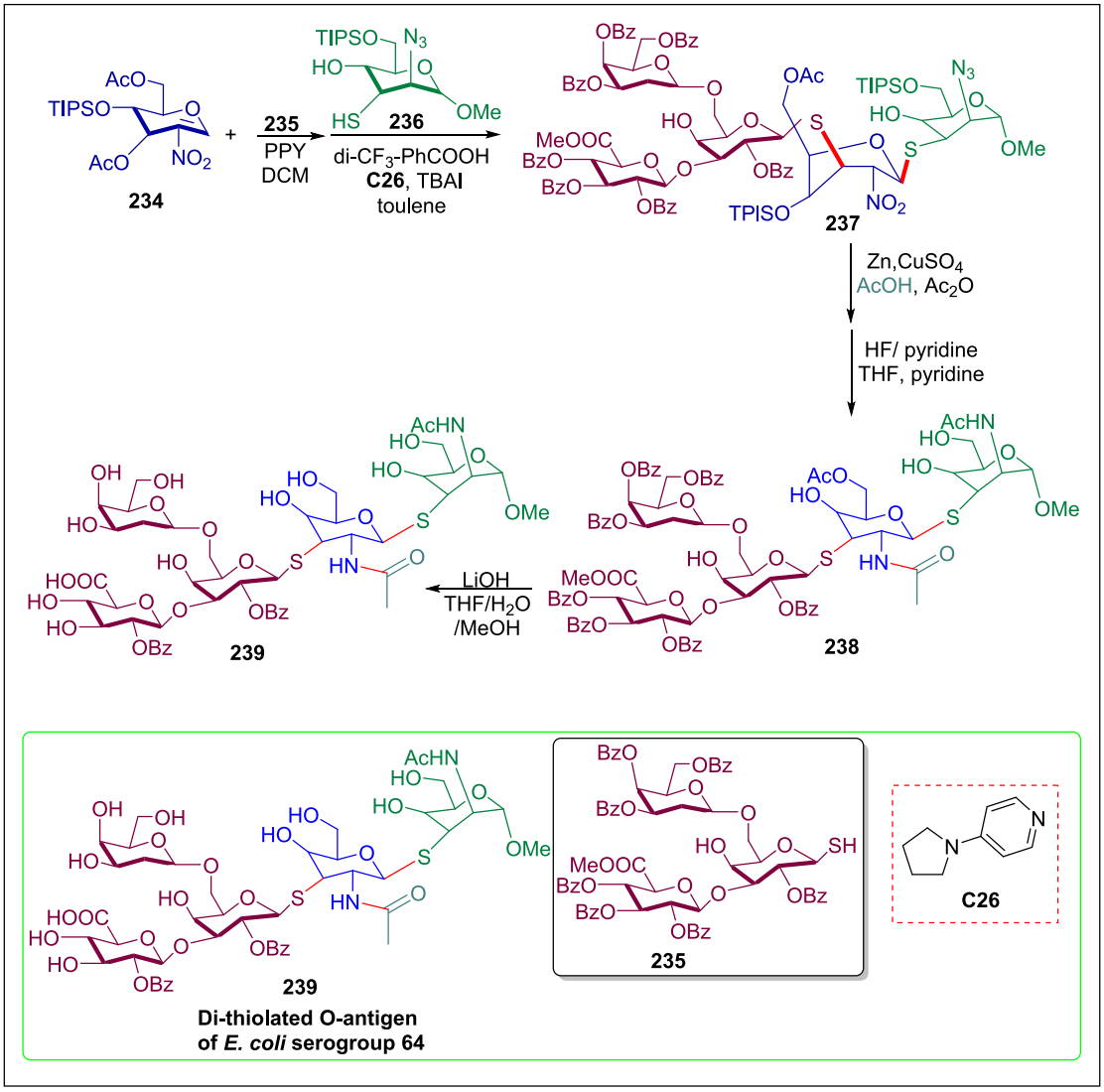


Scheme 31. DABCO catalyzed synthesis of BACE1 inhibitors.



Scheme 32. DABCO catalyzed synthesis of spirocyclopropyl oxindoles.

oxidation of 1-butyl phthalan **276** using α-angelica lactone **C33** as an organocatalyst. The process begins with the acidic proton of **C33** being deprotonated by 4-(Dimethylamino)pyridine, resulting in the dienolate species **278**. This species then takes triplet O_2 to yield the peroxide species (Peixoto et al., 2013), whose homolytic cleavage produces the radical species **279** and **280**. Following the *H*-atom abstraction of **276** by either the alkoxy radical **279** or the peroxy radical **280**, radical species **283** is produced. This species combines with oxygen to produce



Scheme 33. 4-pyrrolidinopyridine catalyzed synthesis of di-thiolated *O*-antigen of *E. coli* serogroup 64.

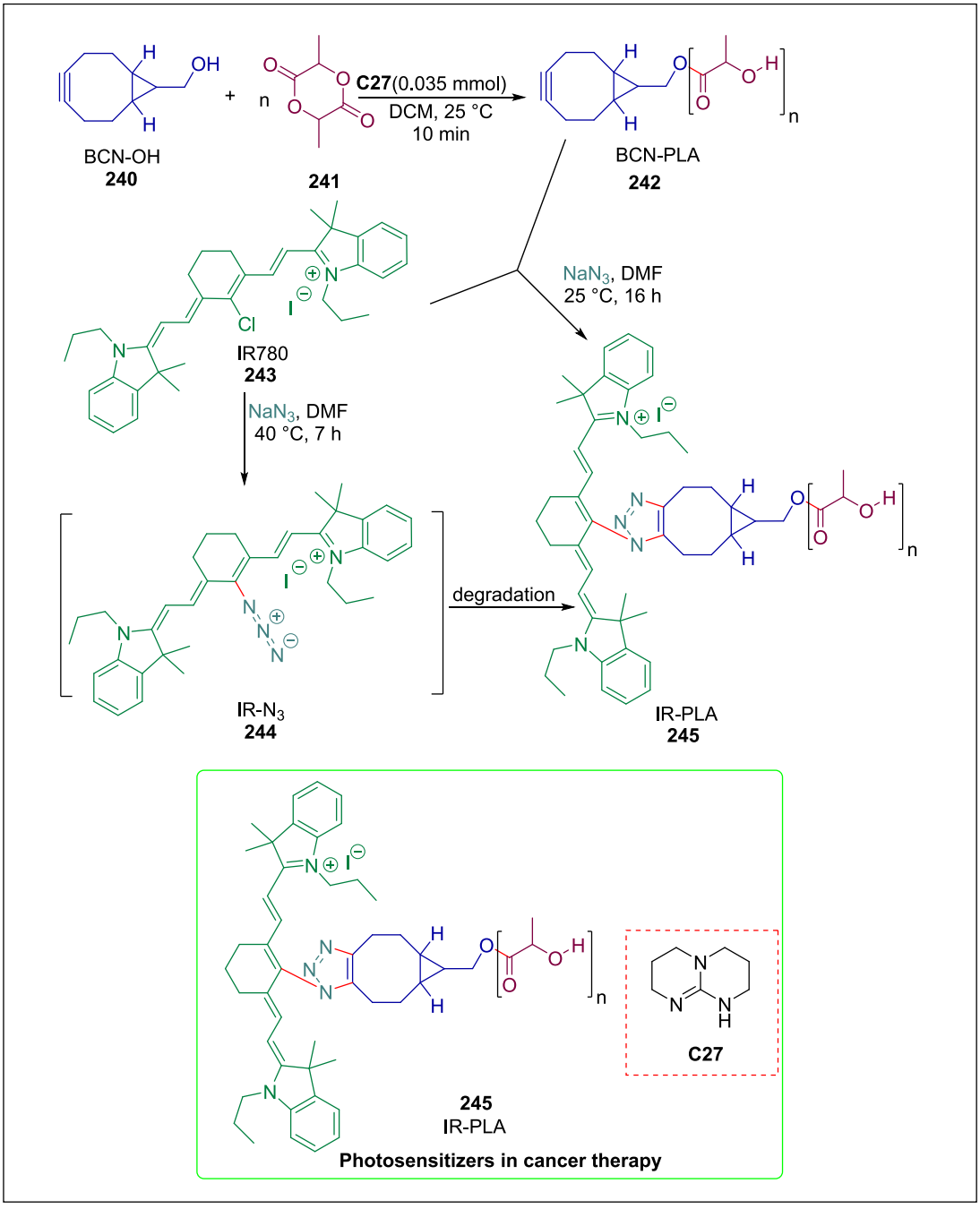
hydroperoxide intermediate **284**, which collapses to product **277** upon additional *H*-removal by the base. On the other hand, a single electron transfer from substrate **276** might produce a radical cation that can then undergo *H*-atom transfer to produce an oxocarbenium ion. This ion then recombines with peroxy radical **280** to produce intermediate **284**, which dehydrates to produce 3-butylphthalide **277** (Scheme 40) (Thatikonda et al., 2020). This approach has the advantage that its reaction conditions work with a variety of cyclic ethers. A formal synthesis of a commercial anti-platelet drug demonstrates the synthetic potential of this new technology.

5.4. Deep eutectic solvent catalyst

The indole ring and its derivatives are now considered unique pharmacophores (Sujatha et al., 2009; Nirmal et al., 2010; Chavan et al., 2011). This ring is also an essential component of indomethacin, an NSAID currently on the market. Harsh chemicals and solvents were used to synthesize indole-type moieties, which resulted in serious health problems and environmental damage (Gomha and Khalil, 2012; Farghaly et al., 2015). Deep eutectic solvent (DES), an alternative to such solvents, is the best option for certain chemical reactions (Singh et al., 2013; Bakht et al., 2016). Imran *et al.* used ultrasound and DES (choline chloride: urea, 1:2) in a multistep reaction involving isatin **285** and thiosemicarbazide **286** to create derivatives of indolin-2-ones **290**. The urea part of DES **C34** catalyzes the reaction by forming H-bonds. Thus, the acetyl moiety of 3-bromoacetylcoumarin **288** is stabilized by urea in a DES through hydrogen bonding. This is then attacked by the amide functional group of hydrazine thioamide **287** to give the vital intermediate **289** in 95 % yield through the cyclization and dehydration process. This intermediate **289** is refluxed from 1 to 3 h in the presence of substituted aromatic amines and formaldehyde and 30 mL of ethylene glycol to synthesize indolin-2-ones derivatives **290** (Scheme 41) (Imran et al., 2020). The high yield, time and energy savings, use of DES, and a green solvent are the advantages of this protocol. The afforded compounds were evaluated for their lipid peroxidation, anti-inflammatory, analgesic, and ulcerogenic properties. In comparison to the reference medicine indomethacin, compounds **290a-d** showed good anti-inflammatory activity, whereas **290e-g** demonstrated extremely good analgesic action with % analgesic activity values of 69.36 ± 0.5845 %, 66.27 ± 1.0072 % and 69.14 ± 0.6892 % respectively(Scheme 42). The active compounds also exhibited lipid peroxidation activities and their ulcerogenicity was far less than the indomethacin.

5.5. P-toluenesulfonic acid catalyst

Since 1,2,3-triazoles are stable in the presence of oxygen, light, and



Scheme 34. TBD catalyzed synthesis of IR-PLA.

moisture, they are significant building blocks for synthesis (Bourne et al., 2004). Triazole scaffolds are found in different kinds of pharmaceuticals (Dalvie et al., 2002; Kharb et al., 2011). Because typical alkenes react slowly or not at all with azides, the synthesis of 1,2,3-triazolines from azides and alkenes is still restricted to highly activated alkenes (Scheiner, 1968; Kadaba and Edelstein, 1990). Repetto *et al.* synthesized 1,2,3-triazoles from the reaction of D-glucono-1,5-lactone **296** catalyzed by *p*-toluenesulfonic acid **C35**. The mechanism involves intramolecular ring closure through a 1,3-dipolar azide-alkene cycloaddition to form a 1,2,3- triazoline, followed by removal of pTsOH, leading to aromatization (Scheme 43) (Repetto et al., 2019). The practical application of this procedure is that triazole compounds are expected to exhibit action as enzyme inhibitors. Additionally, 2-hexenoate derivatives that were partially protected were created as helpful synthetic intermediates. Compounds **304** and **305** are potential enzyme inhibitors and partially unsaturated analogues of polyhydroxindolizidine alkaloids such as castanospermine and swainsonine [43,44].

5.6. *Trifluoroacetic acid catalyst*

The octahydroindolo[2,3-a]quinolizine ring system is the fundamental structure that underpins almost two thousand different natural chemical families. A sophisticated formation of these building blocks using the Pictet-Spengler reaction was reported by You (Wang et al., 2017)and Zhai (Luo et al., 2004). However, the utilization of lengthy and multistep syntheses to prepare the required scaffolds is a serious drawback of current techniques. Srinivasulu *et al.* demonstrated a one-

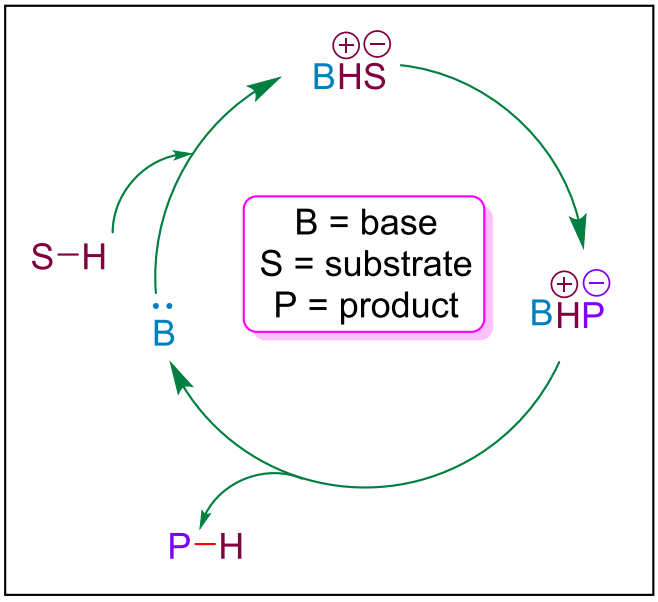


Fig. 3. Mechanism of Bronsted base cataltalysis.

step build/couple/pair technique to synthesize various octahydroindolo [2,3-a]quinolizine derivatives with more than three contiguous chiral centers and a wide diversity of molecular geometries through desymmetrization of the oxidative-dearomatization products of phenols. After the phenol precursor **306** is subjected to Dess-Martin oxidation and hyperiodinate-catalyzed oxidative-dearomatization, cyclohexadione pluripotent building block **307** is produced. This building block then reacts with tryptamine **308** in the presence of organocatalyst TFA **C36** to give intermediate **309**, which is then subjected to aza-Michael addition, resulting in a mixture of the diastereoisomers **310** (Scheme 44) (Srinivasulu et al., 2018). The distinct chemotype compound **310a** that efficiently reduced glycolytic generation of ATP and membrane potential in Hepa1-6 was found most potent compound during the cellular screening of the synthesized compounds library. This compound represents prospective lead therapeutic candidates for the treatment of cancer.

5.7. *Pyridine-2carboxylic acid catalyst*

Substituted imidazoles are employed as powerful BRAF kinase inhibitors (Niculescu-Duvaz et al., 2013), orally active 5-lipoxygenase (5-LO) inhibitors (Mano et al., 2003), and farnesyltransferase inhibitors (Lin et al., 2003). The typical method for synthesizing 2,4,5-trisubstituted imidazoles involves *cyclo*-condensing an aldehyde and ammonium acetate with an *α*-ketomonoxime, *α*-hydroxyketone, or 1,2-diketone. The use of hazardous solvents, a convoluted setup process, challenges with purification, low yield, and costly reagents are some of the disadvantages of this approach. Using pyridine-2-carboxylic acid **C37** as an organocatalyst, Pervaiz *et al.* devised a one-pot, solvent-free formation of 2,4,5-trisubstituted imidazole derivatives **314** through a condensation reaction of substituted aromatic aldehydes **312**, benzil **311**, and ammonium acetate **313**. The reaction begins when **C37**′s proton attacks the carbonyl group of aldehydes **316** and **311**. Next, the protonated carbonyl group of aldehydes is exposed to the nitrogen of NH_3, which binds as a nucleophile to generate the diamine intermediate **318**. This diamine intermediate and protonated benzil **315** condense to give cyclic intermediate state **320** which undergoes [1, 5]-*H* shift to give the trisubstituted imidazoles **321** (Scheme 45) (Pervaiz et al., 2020). This technique stands out for its quick reaction time, ecologically benign synthesis, simple setup, and pure products. To investigate their potential to treat Alzheimer's disease, these afforded compounds were screened against the activity of the acetylcholinesterase (AChE) enzyme. Compounds **321a**, **321b**, **321c**, **321d**, **321e**, **321f**, **321 g**, and **321 h** were all active, but **321 h**, with an IC_{50} value of 102.56 ± 0.14 μM, found to be a strong AChE inhibitor.Scheme 46

Summary

A class of catalysts known as bronsted acid organocatalysts promotes reactions by donating protons (H^+) to the substrates, which increases their electrophilicity and makes them more reactive toward nucleophilic attack. Typically, these organocatalysts have proton-donating acidic functional groups like phosphoric, sulfonic, or carboxylic acids. The mechanism of action generally involves the protonation of a key functional group, such as a carbonyl oxygen or an imine nitrogen, to increase the electrophilic character of the carbonyl carbon or the iminium ion. This protonation accelerates the reaction and decreases the energy barrier for nucleophilic assault (Fig. 4). The application of chiral phosphoric acids in asymmetric catalysis, where the acid not only activates the substrate but also causes stereoselectivity in the product, is a typical example. Bronsted acid organocatalysts are useful in environmentally friendly and sustainable synthesis processes because of their benefits, which include low reaction conditions, great selectivity, and metal-free catalytic cycles. In this section, the synthesis of many bioactive compounds i.e. VNI, the drug-like equivalent of Posaconazole, AChE inhibitors, analgesic, anticancer, antiviral, anti-platelet, and anti-inflammatory compounds via using various organocatalysts such as thiourea, chiral phosphoric acid, α-angelica lactone, deep eutectic solvent, *p*-toluenesulfonic acid, trifluoroacetic acid, and pyridine-2-carboxylic acid catalyst has been described.

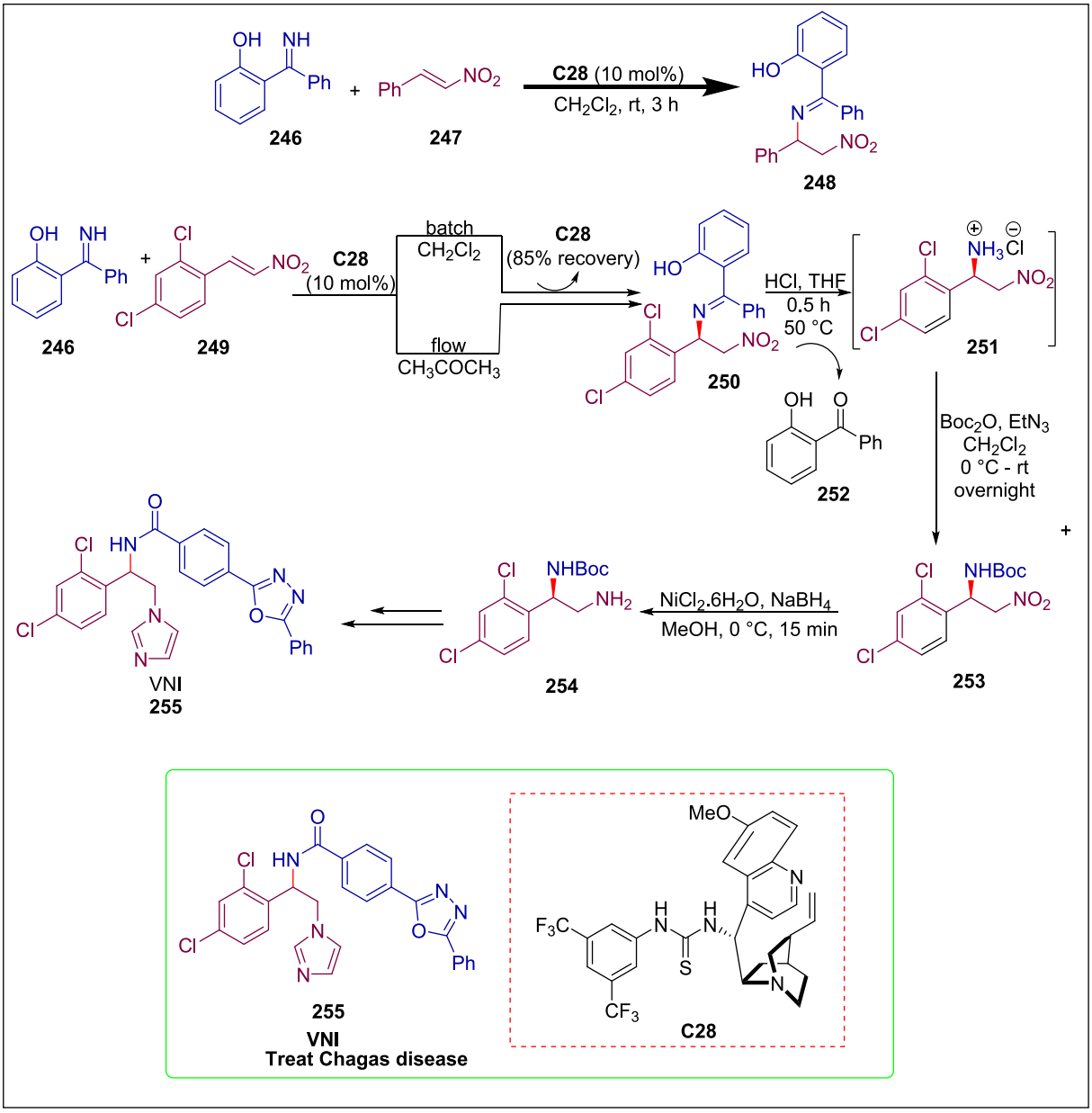
6. Bifunctional organocatalysis

Bifunctional organocatalysts have been applied to numerous asymmetric synthesis processes (Siau and Wang, 2011; Fang and Wang, 2015). In these systems, two different functional groups act synergistically to bring an electrophile and a nucleophile together in a transition state that allows transformations that were previously difficult to carry out (Jiménez et al., 2017). In this type of catalysis, hydrogen-bonding interaction is commonly used. As an illustration, the squaramide, amide, (thio)urea, hydroxyl group, and guanidinium ion are frequently employed as donor functional groups for hydrogen bonding. Through their acidic protons, these groups develop H-bonds with a Lewis-basic moiety in the substrate. In 2021, Zhang *et al.* developed an effective halogen-free and green pathway for forming cyclic carbonates from CO_2 and epoxides by using bifunctional organocatalysts bearing diamine and carboxylic acid groups (Zhang et al., 2021b).

6.1. *Cinchona alkaloids-derived catalyst*

Spirooxindoles are very important skeletal in many pharmacophores. The synthesis of these moieties has been the focus of significant research in recent times in an attempt to expand the boundaries of current drug and probe development (Hong and Wang, 2013; Cheng et al., 2014; Xie et al., 2018). Liu *et al.* synthesized many spirooxindoles derivatives *via* organocatalytic [3 + 2] annulations of the readily available 3-hydroxyoxindoles and pyrrolidone-derived cyclic ketolactams. 3-hydroxyoxindole **322** reacts with pyrrolidone-derived cyclic enone **323** in the presence of chiral bifunctional cinchona alkaloid catalyst **C38** to yield a variety of tetrahydrofuranyl spirooxindole **324** (Scheme 47) (Liu et al., 2021). The one-step assembly of four continuous stereocenters, significant atom economy, and gentle (oxidant-free) reaction conditions are some of the intrinsic benefits of this synthetic technique. The antiproliferative activity of these synthetic compounds was tested. The *N*-unprotected compound **324** remarkably suppressed the growth of MCF-7 breast cancer cells and the gastric cancer cells HGC27 and BGC823.

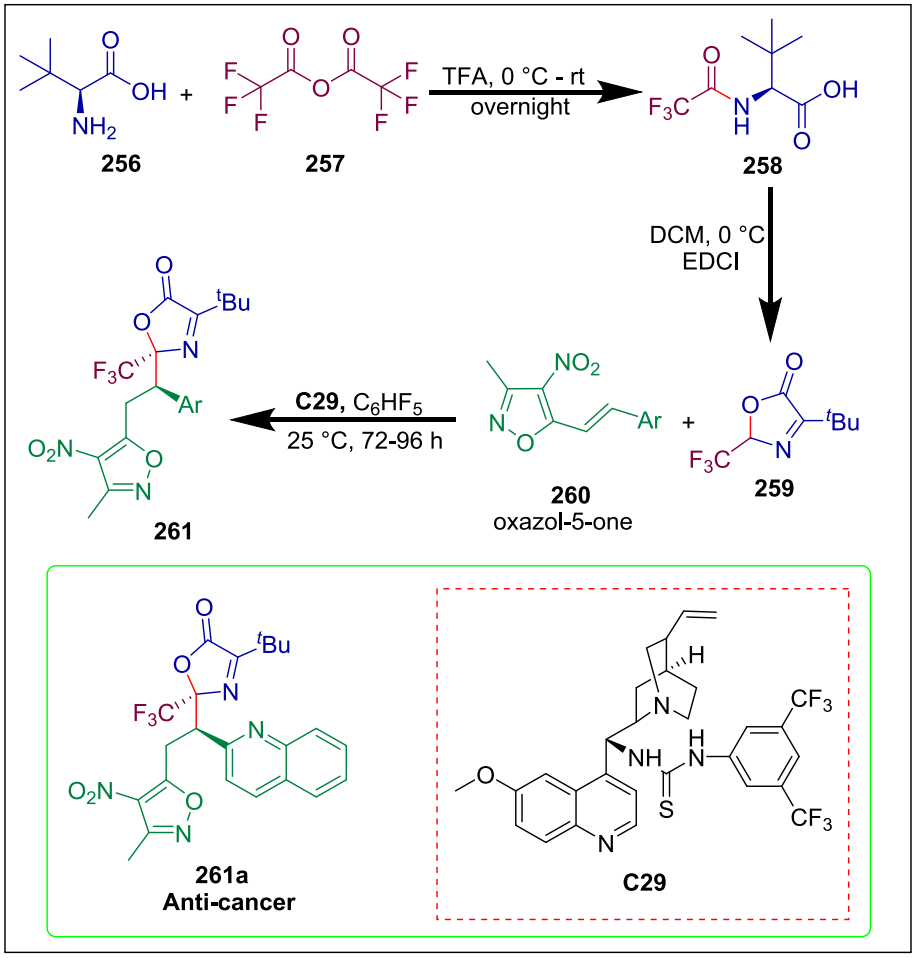
Chiral secondary and tertiary *β*-hydroxy ester frameworks can be found in dicrotaline, atorvastatin, and epothilone B, among other pharmaceutical and natural medicines (Kusumi et al., 2013; Mahrwald,



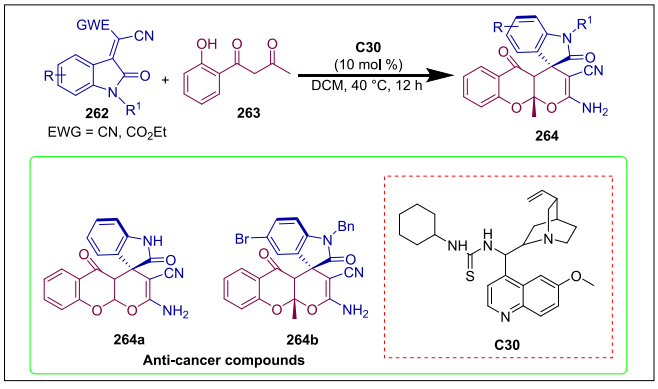
Scheme 35. Takemoto's thiourea catalyzed synthesis of VNI.

2013; Dias et al., 2016; Cheng et al., 2018). In the biosynthesis of polyketides and fatty acids, nature freely employs the enzymatic decarboxylative activation of malonic acid half-thioesters (MAHTs) to produce simple ester enolates or their counterparts (Staunton and Weissman, 2001; Austin et al., 2004; Blaquiere et al., 2009; Bernardi et al., 2012). Drawing inspiration from nature, Park *et al.* effectively used MAHTs as ester enolate equivalents in the organocatalytic decarboxylative aldol reactions of MAHTs **331** with 2,2,2-trifluoroacetoketone **330** to produce enantio-enriched *β*-hydroxy thioesters **332**. Cinchona-based thiourea (CD-TU) **C39**, which is an extremely effective polyketide synthase-mimic catalyst, is utilized in this reaction. In the presence of methanol, *β*-hydroxy thioesters **332** react with amines to form *β*-hydroxy amides, **333**, **334**, and **335**. These amides are essential scaffolds for the development of CF_3 analogues of antidepressant drugs, including (*R*)-tomoxetine, (*R*)-fluoxetine, and (*R*)-duloxetine. *β*-hydroxy thioester **332** can also be easily converted into the trifluoromethylated-analogue **336** of the antidepressant drug fenpentadiol (Elks, 2014; Park et al., 2019) by employing the Grignard process. Furthermore, *β*-hydroxy thioesters **332** also provide access to the ketones **337** and **338**, important intermediates in the production of antiparasitic isoxazoline medicines like fluralaner and afoxolaner, respectively, through Liebe skind-Srogl coupling (Scheme 48) (Park et al., 2019). The easy conversion of the aldol adducts' thioester moiety into various chiral trifluoromethylated *tert*-aldol therapeutic agents highlighted the practical application of the current biomimetic aldol approach.

1,2-Azoles are important building blocks in ligand/catalyst development and are often present in different substantial natural products and pharmaceuticals (Adams, 1960; Vicentini et al., 2007; Lutter et al., 2020; Durand-Reville et al., 2021). Since it is challenging to manage the development of a heterocyclic ring and the atroposelective installation of a stereogenic axis at the same time, the atroposelective technique for 1,2-azoles, such as isoxazole, isothiazole, and its *S*-oxides, has not been examined (Lamers et al., 2016; Zhang et al., 2017; Yu et al., 2018). Chang *et al.* described an organocatalytic novel ring formation method for the synthesis of atropoisomeric naphthyl pyrazoles by using modified vinylidene *ortho*-quinone methide intermediates. This approach



Scheme 36. Quinine-derived thiourea catalyzed synthesis of oxazol-5-ones.

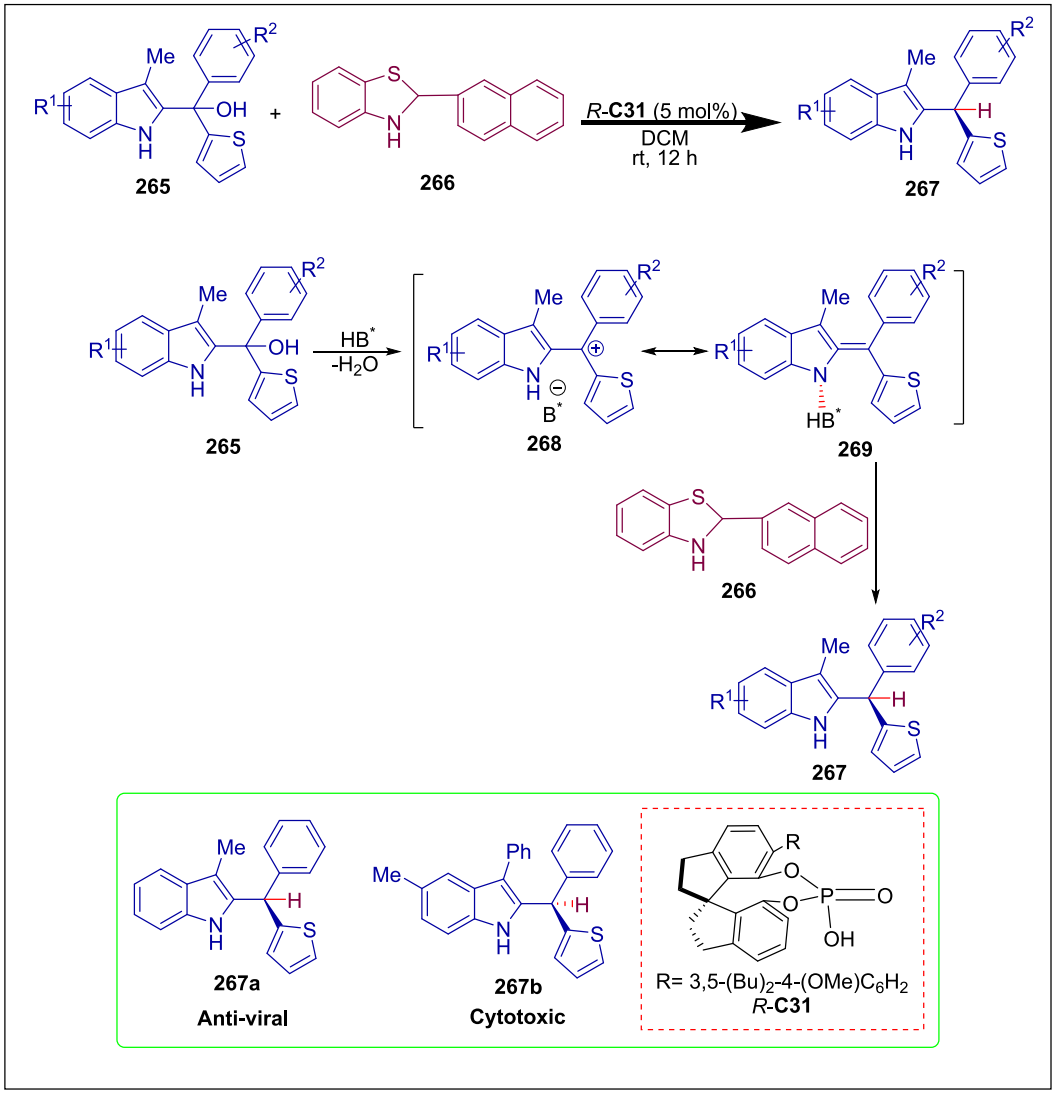


Scheme 37. Quinine-derived thiourea catalyzed spiro oxindole containing a tricyclic pyran-annulated benzopyrans.

offers a simple way to create a variety of atropisomeric heterobiaryls that could not be obtained with previous methods. (*Z*)-*N*'-(1-cyclopropyl-3-(2-hydroxy-7-methoxynaphthalen-1-yl)prop-2-yn-1-ylidene)-P,P-diphenylphosphinic hydrazide **339** reacts with NBS in the presence cinchona alkaloids-derived squaramide **C40** as an organocatalyst to give naphthyl-pyrazole (*N*, *N*-1,2-azole) **340** in moderate to high yields and with high enantioselectivities (Scheme 49) (Chang et al., 2022). In A375 cells, the produced pyrazole **340** with an IC_{50} value of 2.57 μM caused apoptosis and had strong antiproliferative action

Seven-membered cyclic trienes, or tropolones, are a group of aromatic compounds with various bioactivities, including antifungal, antibacterial, and anticancer properties (Pauson, 1955; Morita et al., 2003; Zhao, 2007; Nakano et al., 2015). Hammer *et al.* documented the first organocatalytic approach involving HOMO-activation of tropolones through bifunctional Brønsted-base catalysis. A range of transformations, including photoisomerizations into complex chiral norcaranes, illustrate the synthetic value of the resulting compounds. Tropolone **341** and *N*-propargylmaleimide **342** undergo cycloaddition using the bifunctional Brønsted-base quinine catalyst **C41** to give bridged bicyclic cycloadduct **343** (Scheme 50) (Hammer et al., 2018). Then this synthesized cycloadduct **343** was tested on MCF-7 cancer cells and showed cytotoxic activity.

(*S*)-forphenicinol is the active component of the immunomodulator (Ishizuka et al., 1982)and anticancer (Ishozika et al., 1982)medicine forfenimex. Total synthesis of (*S*)-forphenicinol was previously achieved by condensing 3-methoxybenzaldehyde with an (*S*,*S*)-2,2-dimethyl-5-amino-1,3-dioxane-based chiral auxiliary (Weinges et al., 1987). This approach has some drawbacks, such as low yield (less than 1 %), difficult chiral auxiliary synthesis, and the inability of its recycling due to oxidative damage during deprotection. A more practical and effective approach for the organocatalytic asymmetric formation of (+)-(*S*)-forphenicinol was disclosed by Kovalevsky *et al.* The readily available 2-hydroxy dimethylterephthalate **346** is reduced to diol **347**, which then converts into cyclohexanone-based ketal **348**. Following this, the distant methoxycarbonyl group is reduced to produce hydroxymethylarene **349**, which is then further oxidized to produce aldehyde **350** that is transformed into *N*-protected imine **352**. This Schiff base **352** is subjected to hydroquinine-catalyzed **C42** asymmetric Mannich-type



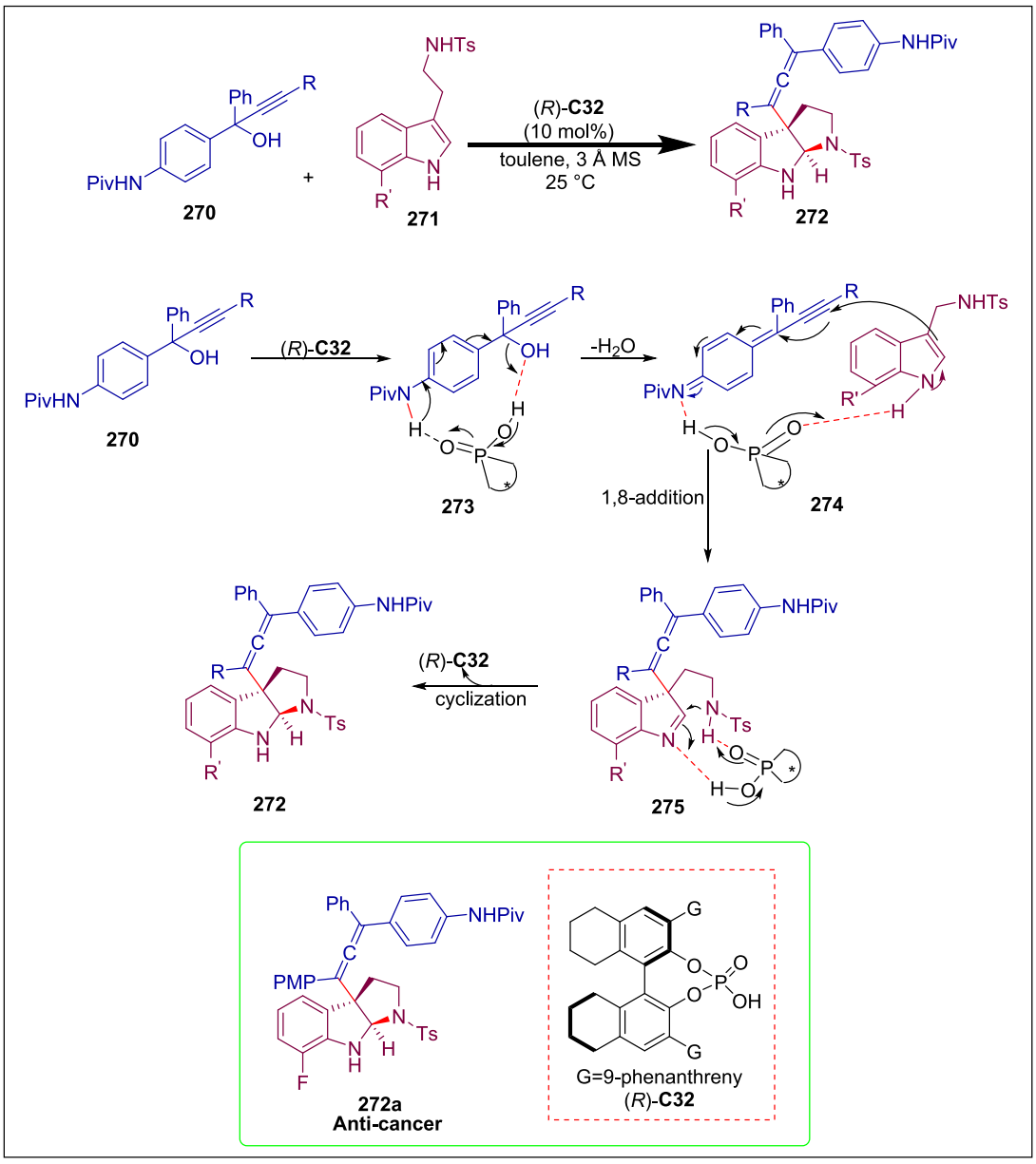
Scheme 38. Chiral phosphoric acid-catalyzed synthesis of triarylmethane.

addition to allomaltol **353** produced from kojic acid. This results in an adduct **354**, which then goes through successive oxidative fragmentation to yield the required enantiomerically pure (*S*)-forphenicinol hydrochloride **355** (Scheme 51) (Kovalevsky et al., 2023). Compared to yields obtained by already-known approaches, the yield obtained by this methodology is much higher (17 %).

Organofluorine scaffolds commonly exist in numerous biologically active natural products and drugs (O'Hagan, 2008; Berger et al., 2011; Hiyama, 2013; Gillis et al., 2015). However, due to the inherent steric congestion, synthesizing vicinally bis(trifluoromethyl)-substituted compounds is a significant problem in current chemical synthesis (Gao et al., 2014; Molander and Ryu, 2014; Yang et al., 2015). To produce the vicinally bis(trifluoromethyl)-substituted spiro pyrrolidine-benzothiophenones **358**, Zhao *et al.* proposed an organocatalytic **C43** asymmetric [3 + 2] cycloaddition of *β*-trifluoromethyl enones **356** with 3-(*N*-2,2,2-trifluoroethyl) benzothiophene ketimines **357** (Scheme 52) (Zhao et al., 2023a). When the cytotoxicity of these produced compounds was tested against the A549 and K562 cancer cells, it was discovered that compounds **358a** and **358b** showed cytotoxicity, with IC_{50} values of 24.91 μM and 45.02 μM respectively.

6.2. Proline catalyst

Phthalimides are biologically active moieties and are included in certain commercial medicines that are used to treat multiple myeloma (Pomalyst), psoriasis (Otezla), and rheumatoid arthritis (Thalomid) (Gutiérrez-Rodríguez, 1984; Del Rosso and Kircik, 2016; Rios-Tamayo et al., 2017). Recent methods for synthesizing phthalimides have included benzannulation processes catalyzed by transition metals (Sheykhan et al., 2017; Yang et al., 2018). The use of transition metals is dangerous due to their toxicity. A simple, atom-efficient, one-pot, environmentally safe method for synthesizing phthalimide derivatives was presented by Akhtar and Lee. They carried out an L-proline catalyzed **C47** reaction between two dienophiles of *α,β*-unsaturated aldehydes **360**, and maleimides **359** to synthesize phthalimide derivatives **361** An effective benzannulation is involved in the reaction, which is carried out by a conventional [4 + 2] cycloaddition of azadiene intermediates produced in situ from *N*-substituted maleimides and enals. At first, *α,β*-unsaturated aldehyde **360** is transformed into iminium ion **362** in the presence of **C44** and phenylmethanoic acid which is further transformed into azadiene intermediate **364** through **363**. After that, the Diels-Alder adduct **365** is obtained by [4 + 2] cycloaddition of **364** with **359**. This adduct then proceeds via L-proline elimination of desired phthalimide **361** (Scheme 53) (Akhtar and Lee, 2020). This approach has the benefit of yielding a wide range of functionalized phthalimides in moderate to exceptional yields, as it is compatible with *α,β*-unsaturated aldehydes, and *N*-substituted maleimides. The synthesis of biologically active compound **361**, which exhibited strong activity



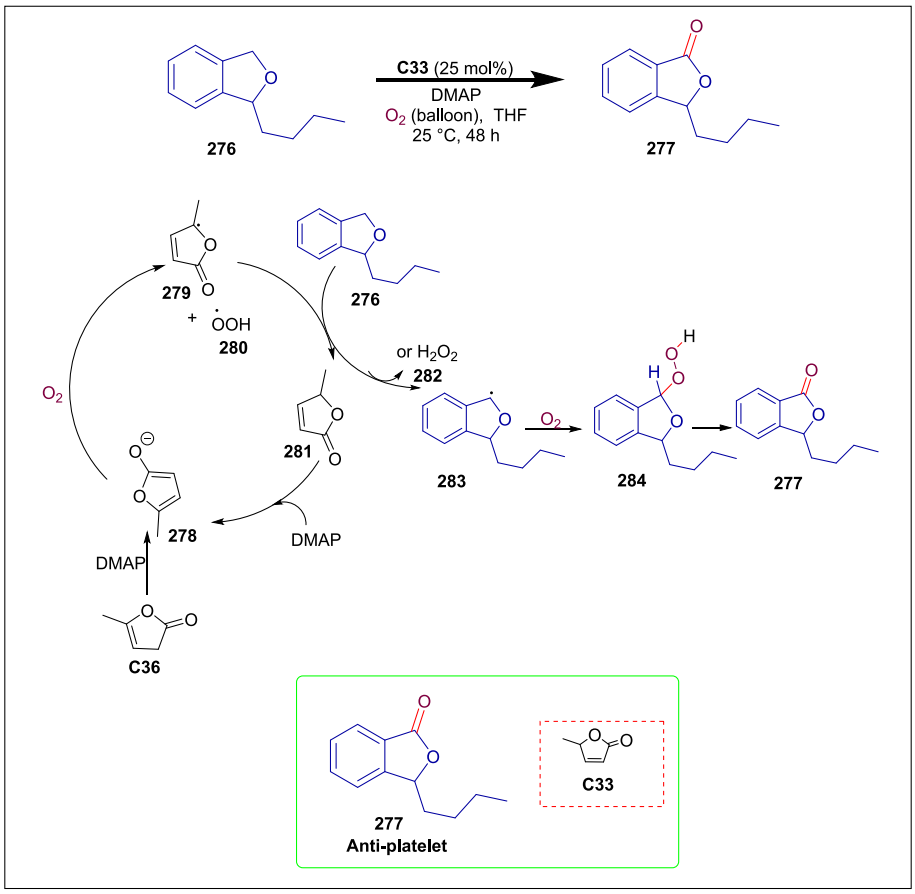
Scheme 39. Chiral phosphoric acid-catalyzed synthesis of chiral allenes.

(IC_{50} = 0.4 μM) as a COX-2 enzyme inhibitor, validates the importance of this effective procedure. (Alaa et al., 2011).

6.3. Prolinol catalyst

Sphingosine kinase (SPHK) inhibitors are promising therapeutic agents because SPHK1 is typically up-regulated in different cancer types and its genetic ablation makes cancer cells more susceptible to chemotherapeutic agents (Shida et al., 2008; Takabe et al., 2008; Gault and Obeid, 2011; Santos and Lynch, 2015). Casao *et al.* devised an effective method h for generating enantioenriched alkynylaziridines by using a prolinol-catalyzed aziridination reaction of *α*; *β*-unsaturated aldehydes followed by homologation reaction. This method produced a series of sixteen sphingosine analogues with a common triazole scaffold. The process begins with monoprotected diol **366** oxidizing to *α*,*β*-unsaturated aldehyde **367**, which then goes through an aziridination reaction catalyzed by Tetramethylsilane −protected diphenylprolinol (*R*)-**C45** (Jensen et al., 2012) to yield *β*-formyl aziridine **368**. Then **368** undergoes Corey-Fuchs conditions to afford dibromoalkene **369** which gives ethynylaziridine **371** through metal-halogen exchange and ulterior *α*-elimination. After aziridine **371**′s ring opens, **372** is produced, which goes through basic hydrolysis to produce the *N*-protected amino alcohol **373**. 1-Azidododecane **378** is produced when 1-bromododecane **376** reacts with sodium azide **377**. The corresponding azido aldehyde **383** undergoes a Wittig reaction with corresponding trifluorinated phosphorus ylide **382** to give azide **384** (Scheme 55). Next, the azides **378** and **384** undergo a cycloaddition reaction with the alkyne **373** to produce triazoles **374**. These triazoles are then converted to the required *N*-Boc derivatives **375** (Scheme 54) (Escudero-Casao et al., 2018). The in vitro activity of the synthesized compounds as SPH inhibitors was examined and all compounds except two show activity. But two of them (**375a** and **375b**) demonstrated an IC_{50} value near to that of standard inhibitor *N*,*N*-dimethylsphingosine (DMS) whose IC_{50} values for SPHK1 for SPHK2 are 27.3 μM and 3.8 μM respectively. Compound **375a** exhibited an IC_{50} = 7.9 μM for SPHK2 while compound **375b** was the most potent in this series in terms of activity with IC_{50} values of 60 μM and 18.1 μM for SPHK1 for SPHK2 respectively.

Reboxetine is an antidepressant drug. It is also useful in the



Scheme 40. *α*-angelica lactone catalyzed synthesis of 3-butylphthalide.

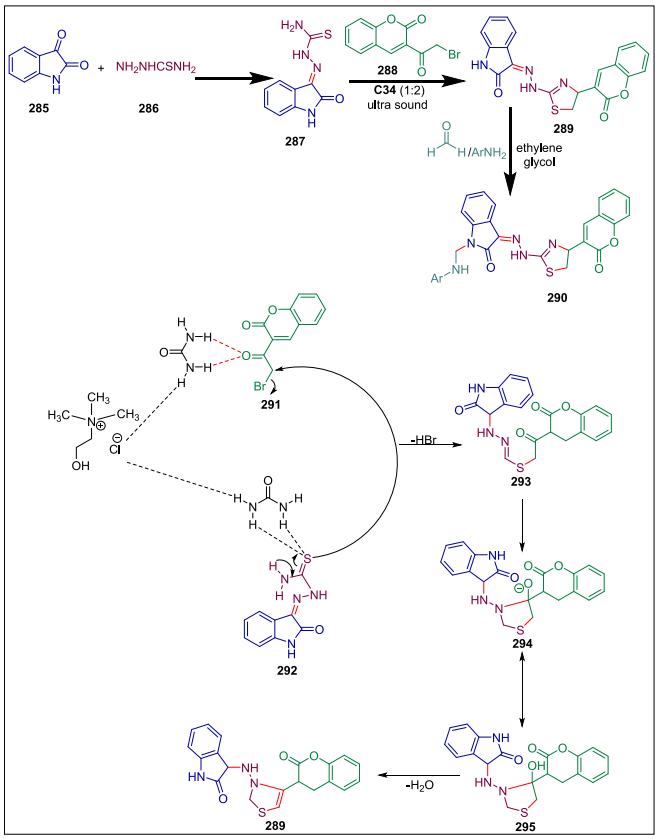
treatment of narcolepsy, panic disorder, ADHD (attention deficit hyperactivity disorder) (Melloni et al., 1984; Hajós et al., 2004), and cocaine dependence diseases (Ghanizadeh, 2015; Sharma and Pandey, 2022). It was previously synthesized using chiral starting materials, protection, deprotection, and multistep techniques. By using *trans*-cinnamaldehyde, Sharma and Pandey devised an effective, straightforward, and succinct prolinol-catalyzed protecting-group free synthetic approach for the total synthesis of (*S*,*S*)-reboxetine **394** and (*S*,*R*)-reboxetine **391**. The asymmetric synthesis of **394** and **391** is started with *trans*-cinnamaldehyde **385**, which upon treatment with H_2O_2 and tris-buffered saline-protected (*R*-bis[3,5- bis(trifluoromethyl)phenyl]prolinol **C46** organocatalyst followed by subsequent reduction affords 2,3-epoxy-1-ol **386**. The OH group of the epoxide compound **386** changes into *O*-mesylate, which experiences an epoxide opening at the C-3 position. After undergoing a K_2CO_3 treatment in MeOH and configuration inversion, compound **387** (Behrens and Sharpless, 1985) is produced which is then treated with 2-ethoxyphenol to produce the required (*S*,*S*)-epoxy ether **392** that undergoes the regioselective ring-opening with 2-aminoethyl hydrogen sulfate and 1,8-Diazabicyclo[5.4.0]undec-7-ene as the base to afford the zwitterion **393**. Finally, compound **393**′s cyclization under basic circumstances yields (*S*,*S*)-reboxetine **394**. Under Mitsunobu esterification conditions, intermediate **381** may also offer a parallel route to the synthesis of **391** through configurational inversion at the C-3 position (Mitsunobu, 1981; Lipshutz et al., 2006), followed by basic hydrolysis (Scheme 56) (Sharma and Pandey, 2022).

6.4. *β-amino alcohol catalyst*

Quinagolide **407** is a drug used to treat high prolactin levels. It combines the structural characteristics of ergolines CQ 32–084 (Satoh et al., 2007), pergolide (Barbe et al., 2011), and apomorphine (Kim and Batey, 2018), three common dopamine agonists. To date, enantioselective total synthesis of (−)-quinagolide **407** is not reported. Chavan *et al.* presented a completely different methodology for the total synthesis of (−)-quinagolide **407** (Chavan et al., 2018; Chavan et al., 2019b) from pyridine **395** by using racemic *β*-amino alcohol **C47** (Suttibut et al., 2011)as an organocatalyst. The main steps used in the synthesis are organocatalyzed Diels-Alder reaction for fixing all three stereocenters on the piperidine ring, Birch deoxygenation, Lewis acid ($TiCl_4$) catalyzed intramolecular Friedel-Crafts cyclization of dicarboxylic acid **401**, and one-pot diastereoselective ketone reduction-intramolecular cyclization to synthesize tetracyclic oxazolidinone **403** that gives the desired *trans*-geometry (Scheme 57) (Chavan et al., 2019a). It has been found that under Birch reduction conditions, a C-N bond in an electron-deficient isoquinuclidine scaffold cleaves reductively. This is the first synthetic attempt to obtain the (−)-quinagolide **407** core framework.

6.5. *Chiral carbamate catalyst*

Remdesivir, an RNA-dependent RNA polymerase inhibitor, has been employed in the treatment of COVID-19 (Cho et al., 2012; De Wit et al., 2020; Wang et al., 2020). Remdesivir is difficult to synthesize, and the net cost is very high. In particular, to achieve the required diastereoisomer (39 %) for subsequent coupling with the D-ribose-derived 5-alcohol, the stereoselective assembly of the P-chirogenic center needs recrystallization of a 1:1 isomeric *p*-nitrophenylphosphoramidate mixture multiple times. Gannedi *et al.* designed one-pot synthesis of remdesivir **384** by using chiral carbamate **C48** as organocatalyst for stereoselective (*S*)-P-phosphoramidation employing a 1:1 diastereomeric mixture of phosphoramidoyl chloridates as the coupling reagent to prevent a waste of the other diastereomer. In the presence of catalyst **C48**, phosphoramidoyl chloridates **408** and D-ribose-derived 5-alcohol



Scheme 41. DES catalyzed synthesis of indolin-2-ones.

409 are coupled in a 1:1 mixture which is subsequently subjected to acidic hydrolysis in *p*-TSA to remove isopropylidene group, to yield a mixture of **410** and its (*R*)-diastereomer, which is further purified by recrystallization to obtain remdesivir **410** (Scheme 58) (Gannedi et al., 2021).

Summary

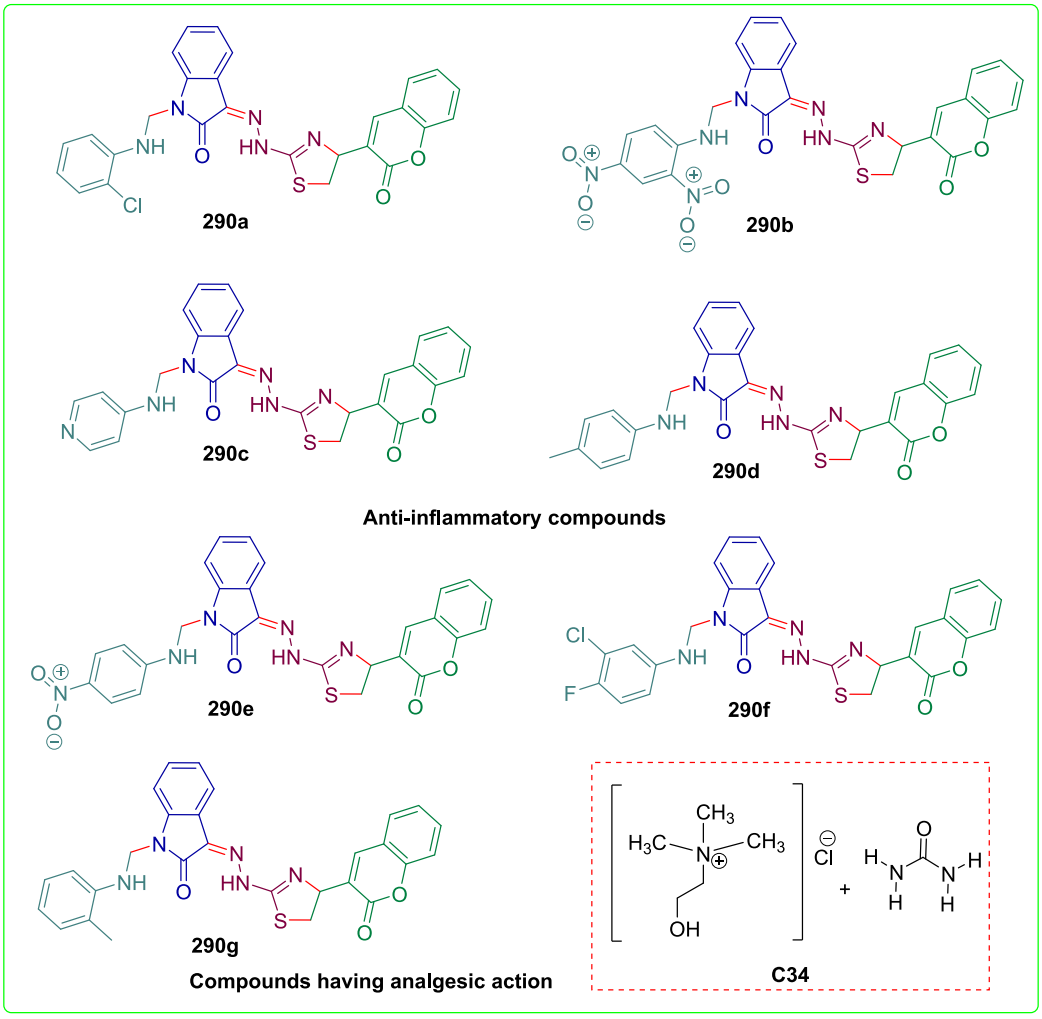
Bifunctional organocatalysts are a special kind of catalysts that can simultaneously activate the electrophile and nucleophile in a reaction because they have both an electrophilic/acidic site and a nucleophilic/basic site. The catalyst's ability to cooperate with both reactants through dual activation increases the rate and selectivity of the reaction. A typical bifunctional organocatalyst has a basic group (imidazole or amine) paired with a hydrogen-bond donor (like a thiourea or squaramide group). In their mechanism of action, the acidic site, often a hydrogen bond donor, interacts with the electrophile such as a carbonyl group by stabilizing its partial negative charge. At the same time, the basic site deprotonates the nucleophile and generates a more reactive nucleophilic species. Simultaneously activating both reaction partners lowers the activation energy and facilitates reactions (Fig. 5). By avoiding harmful metals, operating in mild environments, and promoting extremely selective, effective reactions with little waste, bifunctional organocatalysts serve as green catalysts. Their capacity to be recycled and utilized in non-toxic solvents contributes even more to their environmental sustainability. This section covers the usage of a variety of bifunctional organocatalysts i.e. proline, prolinol, β-amino alcohol, chiral carbamate, and cinchona alkaloids-derived catalysts for the synthesis of many bioactive compounds such as analogous of (*R*)-tomoxetine, (*R*)-fluoxetine, and (*R*)-duloxetine, analogous of antidepressant drug fenpentadiol, fluralaner, afoxolaner, (*S*)-forphenicinol, reboxetine, remdesivir, quinagolide, COX-2 enzyme inhibitors, SPHK inhibitors, and anticancer compounds.

7. Organo-photo catalysis

Photocatalysis under UV activation facilitates the formation of a wide range of unconventional bonds in organic synthesis (Snyder et al., 1981; Dugave and Demange, 2003; Koike and Akita, 2016). Visible light photocatalysis, which offers mild conditions and high functional group tolerance, has recently become a popular approach for activating small molecules. In this case, the light-absorbing photocatalyst is primarily responsible for starting the chemical reaction (Zeitler, 2009; Meyer et al., 2016; Ochola and Wolf, 2016; Shaw et al., 2016; Hu et al., 2017; Zhan and Li, 2017). The use of visible light is a cheap, energy-efficient, and environmentally benign way to stimulate reactions (Brooks et al., 2013; Hager and MacMillan, 2014; Tasker and Jamison, 2015). It is also intriguing to consider using single-electron transfer (SET) pathways, which are made possible by visible light absorption, to speed up molecular activation at low temperatures. In contrast to traditional thermal conditions, the use of single electron transfer in conjunction with a catalyst enables the use of mild reaction conditions to generate required products in excellent yield for a wider substrate scope (Zuo and MacMillan, 2014). Even though the use of SET in photocatalysis has advanced significantly, more research is still needed to understand the photophysical characteristics of these systems and how they relate to catalytic efficiency. This will help to reveal crucial aspects of photocatalyst design (Ochola and Wolf, 2016). In 2020, Chu *et al.* synthesized heterogeneous organo-photocatalysts single-step coupling reaction of eosin Y (EY) with commercial cotton threads. Then the immobilized EY is used for photoinduced organic conversions and reversible deactivation radical polymerization over several reaction cycles with well-retained catalytic efficiency (Chu et al., 2020).

7.1. 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene photocatalyst

A popular methodology for C–H functionalization of heteroarenes is the Minisci reaction (Minisci et al., 1989; Minisci et al., 1990; Duncton, 2011). Radical precursors and photoredox chemistry have been used to generate several latest variants of the Minisci reaction. Recently Okada (Okada et al., 1988; Okada et al., 1991) and Overman (Schnermann and Overman, 2012; Müller et al., 2015; Pratsch et al., 2015; Jamison and Overman, 2016) produced alkyl radicals by subjecting *N*-(acyloxy) phthalimides (NAPs) to light in the presence of a photosensitizer (Okada et al., 1988). An external oxidant is needed for the reductive production of radicals in this approach. To circumvent the need for an external oxidant and the usage of costly metal-based catalysts such as iridium-based complexes, Sherwood *et al.* accomplished the Minisci reaction using an organic photocatalyst **C49**. In their one-pot Minisci approach, they started with a carboxylic acid **411** that acts as a radical precursor and then undergoes NAP synthesis in situ. After that, they add a heteroarene **412** and photocatalyst **C49**. This technique avoided the requirement to isolate a pre-functionalized alkyl partner and allowed for the quick production of analogues employing a group of chemicals which are widely accessible in a high degree of structural variety. The process begins when NAP **415** uses single-electron transfer (SET) to oxidatively quench the excited photocatalyst. This leads to reductive fragmentation, which produces the alkyl radical **417** along with CO_2 and phthalimide **416**. By attacking a protonated heteroarene **418**, radical intermediate **417** produces an adduct **419**, which is then deprotonated to produce α-amino radical **420**, which then undergoes single-electron transfer with the photocatalyst's oxidized form to produce the desired protonated product **421**, which ends the catalytic cycle (Scheme 59) (Sherwood et al., 2018). The benefits of this approach are low conditions, a high level of functional group tolerance, and a low requirement of the carboxylic acid reactant. The synthesis of analogues of camptothecin **414**, an anticancer drug, in 17 % yield using late-stage functionalization of the produced molecules **413** illustrates the practical application of this methodology.



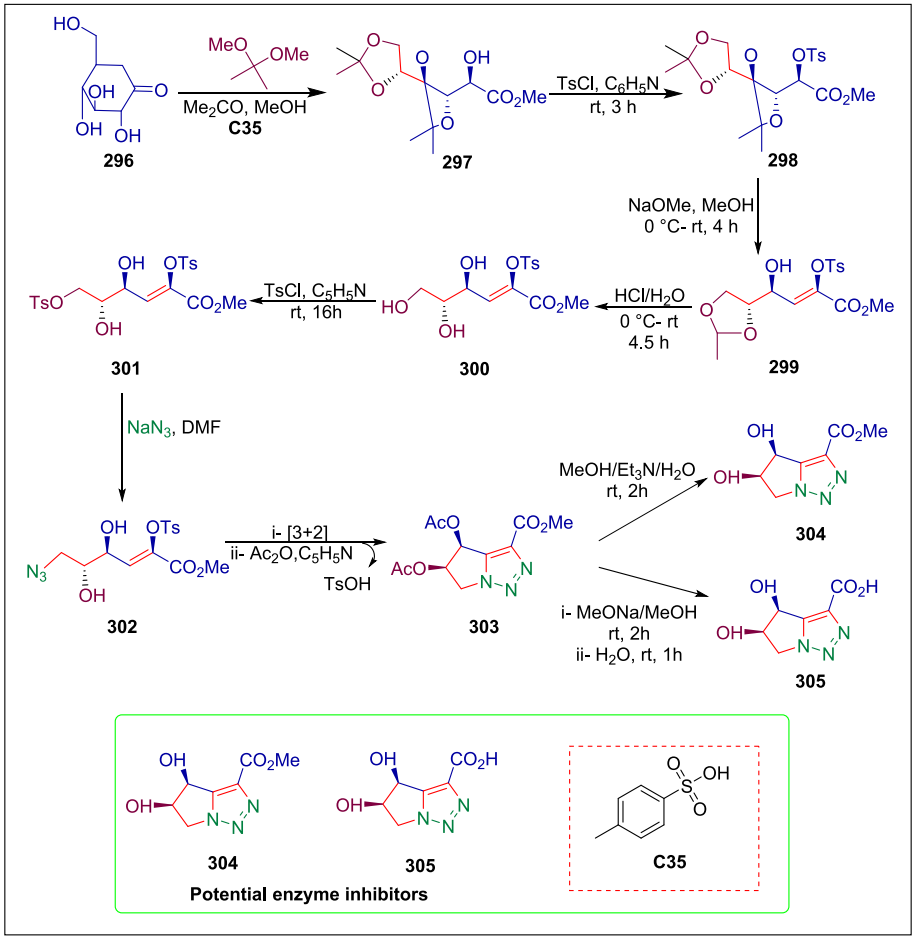
Scheme 42. Structures of bioactive indolin-2-ones.

7.2. Carbazolic-cyano conjugated microporous polymer (CC-CMP) photocatalyst

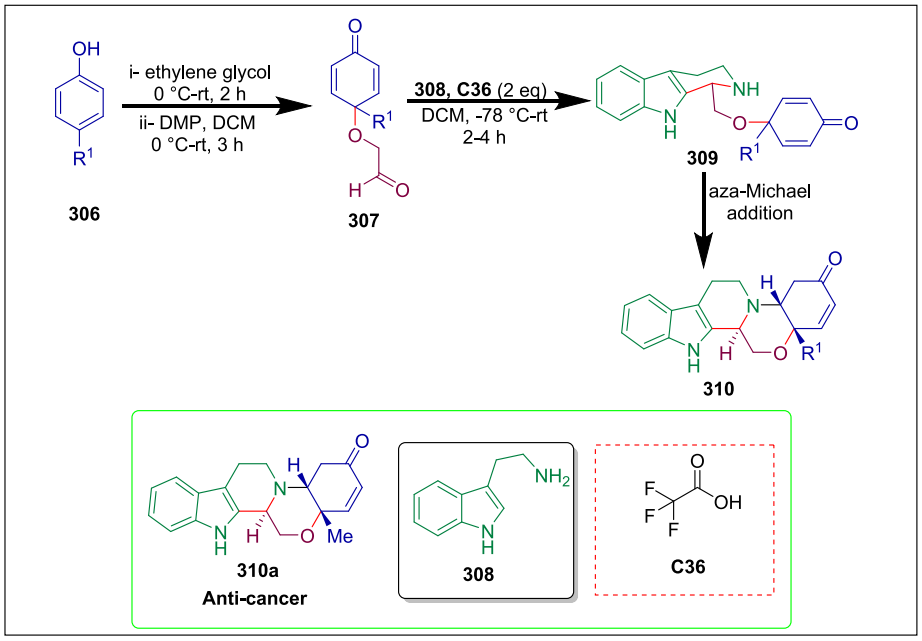
Natural products often contain heterocycle-fused indolines and spirocyclic oxindoles, which have a variety of pharmacological characteristics, including anticancer, antimigraine, and contraceptive effects. Because of this, these moieties are being valued for use in drug discovery and as building blocks in the synthesis of other alkaloids and drugs. But the majority of current synthetic approaches depend on developing vital fused indoline and spirocyclic oxindole skeletons using indole precursors.These methods are not widely applied because they require costly noble-metal catalysts and tedious procedures. Ou *et al.* developed a quick way to produce 3-formyloxindoles **424** by using a heterogeneous organophotocatalyst **C50** and double C–H functionalization of *N*-arylacrylamides **423** and 1,3-dioxolane **422** in a metal-free, light-mediated process. The photoexcited catalyst undergoes SET to TBHP and gives a *tert*-butyloxy radical. After that, the *tert*-butyloxy radical's regioselectivity removes a proton from the carbon 2 of 1,3-dioxolane **422** to form radical specie **425** (Fan et al., 2018). This radical specie then combines with acrylamide **423** to form radical specie **426**, which undergoes intramolecular cyclization to produce radical intermediate **427**. By oxidizing radical intermediate **427** with $PC^{\bullet+}$, the dioxolane acetal intermediate **428** is formed, and aromaticity is subsequently restored. Acidic hydrolysis ultimately affords the requisite product **424** (Scheme 60) (Ou et al., 2019). This approach demonstrates the great potential of using CMPs as stable, reusable, and metal-free light-triggered photocatalysts that provide a sustainable means of producing therapeutic compounds and bioactive heterocycles. Compared to multistep processes, the resulting 3-formyloxindoles are more suited for the rapid synthesis of certain pharmaceutically necessary products, such as (±)-desoxyeseroline, (±)-esermethole, and (±)-*N*-methylerulescine.

7.3. Lumiflavin photocatalyst

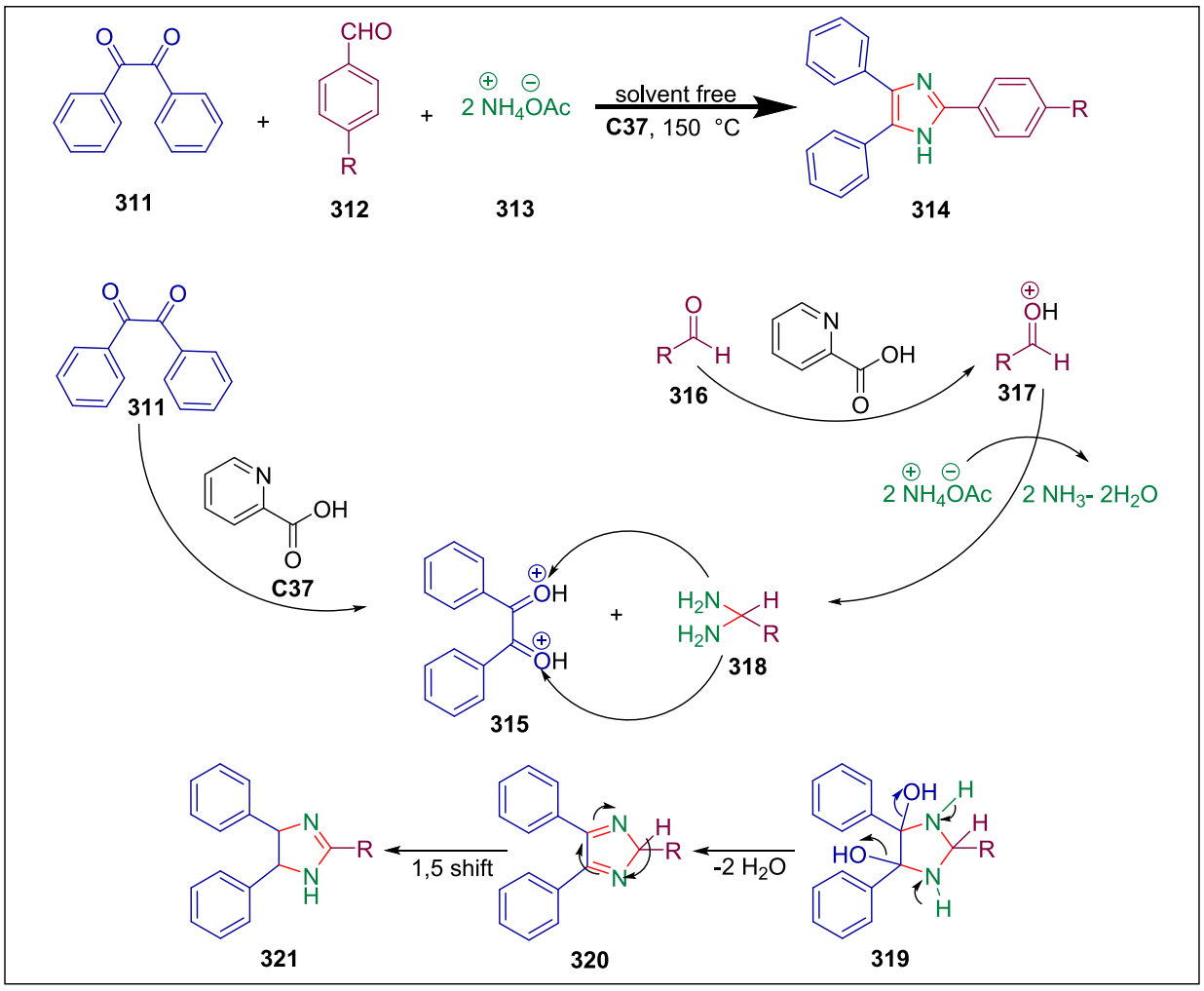
Carbon-centered radicals are essential components of advanced synthetic chemistry. Visible light organophotoredox catalysis has emerged as a potentially effective method for obtaining C-centered radicals from a wide range of latent functional groups, such as boronic acids. Chilamari *et al.* described an aqueous approach that used a organophotocatalyst lumiflavin **C51** to convert aliphatic, aromatic, and heteroaromatic boronic acids **429** to *C*-centered radicals **433**. Through open-shell conjugate addition to various Michael acceptors, these radicals were utilized to produce a broad pool of alkylated products **431**, including three molecules with pharmacological significance. Boronic acid **429** coordinates with water to give aqua-boryl complex **432**. The excited lumiflavin abstracts proton and an electron from **432** then **432** underwent fragmentation to afford heteroaryl radical **433**. With the addition of openshell conjugates to diethyl ethylidene malonate (DEEM) **430**, the former is rapidly captured. This results in the α-malonyl radical **434**, which is then reduced to give the desired alkylated product **431**, and the organophotocatalyst is regenerated (Scheme 61) (Chilamari et al., 2020).



Scheme 43. . *p*-toluenesulfonic acid-catalyzed synthesis of 1,2,3-triazoles.



Scheme 44. Triflouroacetic acid-catalyzed synthesis of spirocyclic pyrazolone-ferrocene hybrids.



Scheme 45. Pyridine-2-carboxylic acid-catalyzed synthesis of 2,4,5-trisubstituted imidazoles.

7.4. Anthraquinone (AQ) photocatalyst

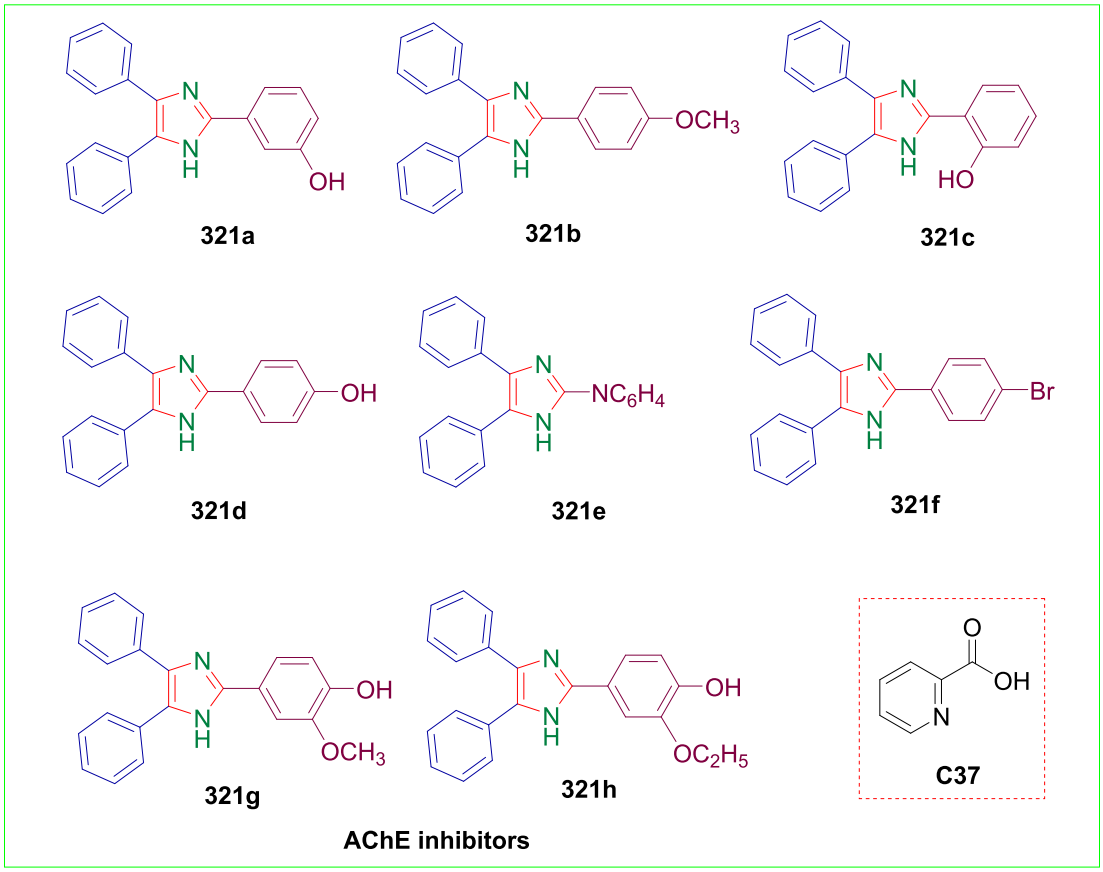
Quinoline has been considered a remarkable motif because of its promising biological properties, which have been demonstrated by approved pharmaceuticals including pitavastatin, cinchophen, camptothecin. Zhao *et al.* described the organophotocatalyzed synthesis of quinolines **437** through cyclizing secondary alcohol **436** into 2-aminobenzyl alcohols **435** at room temperature. By using DMSO and readily available anthraquinone as photocatalyst **C52** this technique removesthe need of high thermal conditions and toxic metal catalysts. A hydrogen atom is extracted from **435** or **436** by the excited photocatalyst AQ via hyrdrogen atom transfer (HAT), producing **438** or **440** radicals, followed by another HAT to yield 2-aminobenzaldehyde **439** or acetophenone **441**. Then protonated AQ is oxidized to AQ by the DMSO. Ultimately, condensation occurs between **439** and **441** to create the desired product **437** (Scheme 62) (Zhao et al., 2023b).

7.5. Eosin Y photocatalyst

Indoles provide a wide range of bioactivity (Cerecetto et al., 2005)to the pharmaceutical sector, including antibacterial, anti-inflammatory, HIV protease inhibition, and anticancer medicines. Commercially significant pharmaceutical drugs like MK-4827 and pazopanib have indazole as a fundamental scaffold. The majority of cases of arylation by arylhalides and Negishi cross-coupling required expensive ligands, Cu/Pd as catalysts, and the use of base and oxidant as additives with long reaction durations. Therefore, there is less research available on the direct arylation of 2*H*-indazoles at the C-3 position. Vidyacharan *et al.* synthesized liver X-receptor inhibitor drugs **444** without converting DIPEA into its radical cation, and they proposed a simple, sustainable method for direct C-3 arylation of 2*H*-indazoles **442** with aryldiazonium salts **443** under milder conditions using organo-photoredox catalysis with green light. By synthesizing the aryl radical **445** and recovering the photocatalyst **C53**, the SET from reduced photocatalysts completes the catalytic cycle. After reacting with heteroarene **442** the resultant radical moiety **445** yields radical intermediate **446**, which is then converted to carbocation intermediate **447** by donating electrons to the *N*,*N*-Diisopropylethylamine (DIPEA). The system is aromaticized during deprotonation, producing the desired product **444** (Scheme 63) (Vidyacharan et al., 2019). High yields were obtained with the phenyl moiety containing electron-donating groups, but very low yields were obtained with bromosubstitution.

Summary

A type of catalyst known as photo-organocatalysts uses visible light as a sustainable and environmentally friendly energy source to drive organic reactions. These catalysts, often organic molecules with conjugated structures, absorb light and achieve an excited state, enabling them to transmit electrons or energy to reactants. The mechanism of action generally involves generating reactive intermediates, such as radicals or excited-state species, which can then participate in bond-forming or bond-breaking processes (Fig. 6). For example, a photo-organocatalyst can absorb light and enter an excited triplet or singlet



Scheme 46. Structures of bioactive 2,4,5-trisubstituted imidazole.

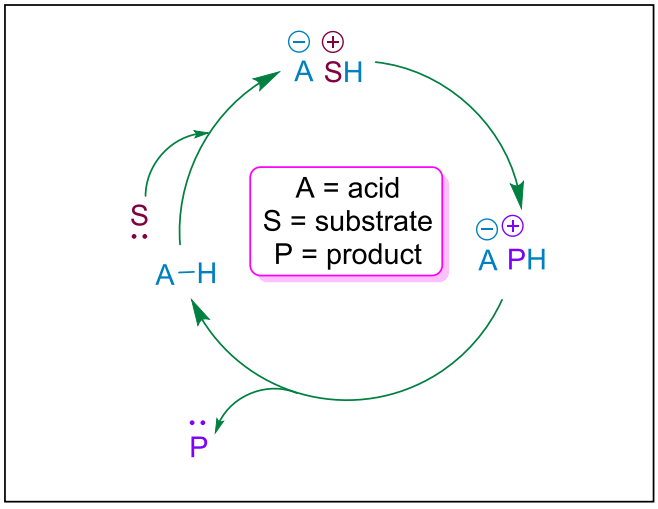


Fig. 4. Mechanism of Bronsted acid catalysis.

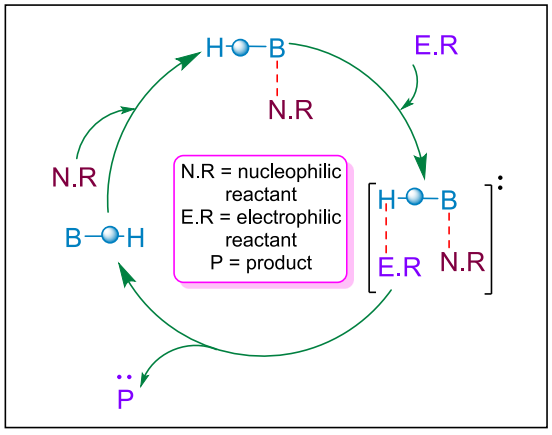
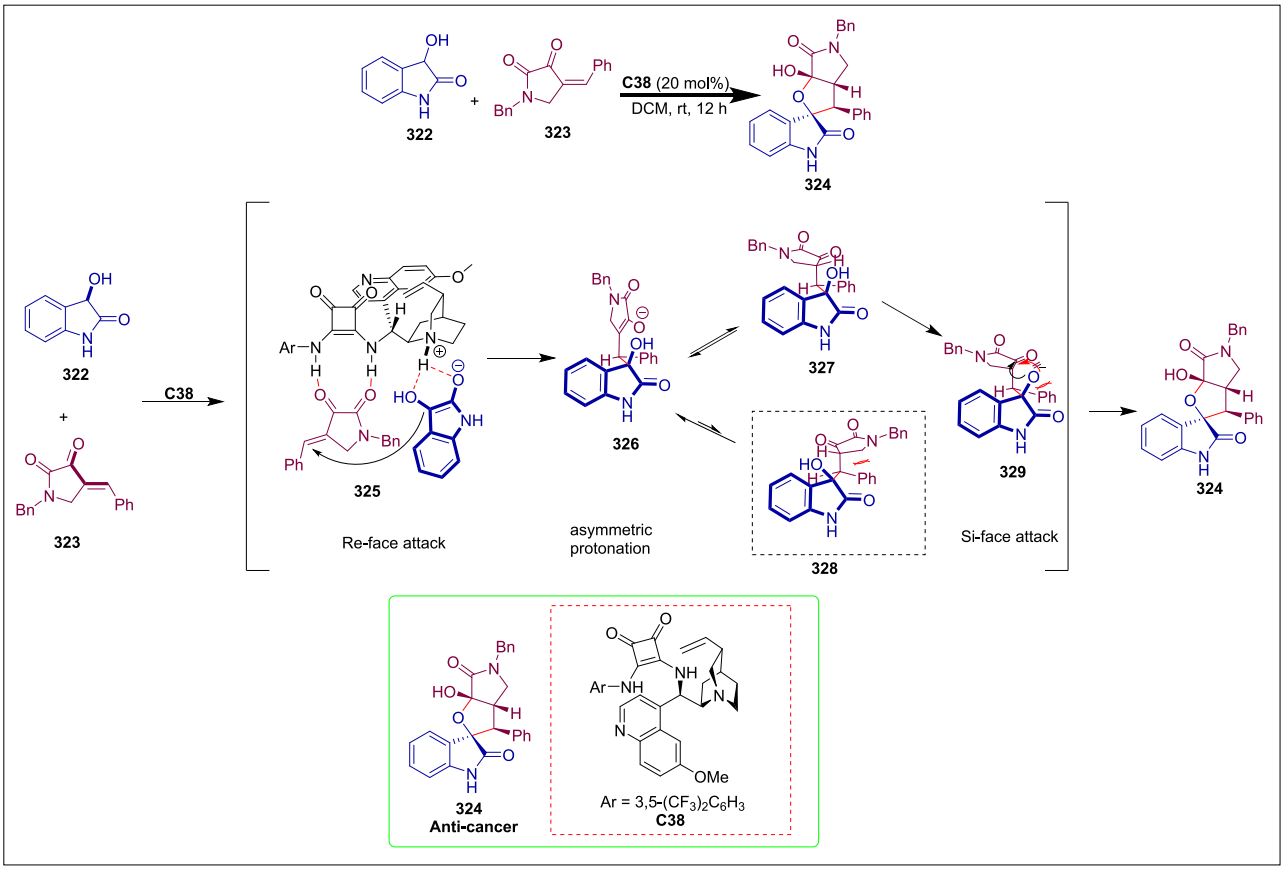


Fig. 5. Mechanism of bifunctional organocatalysis.

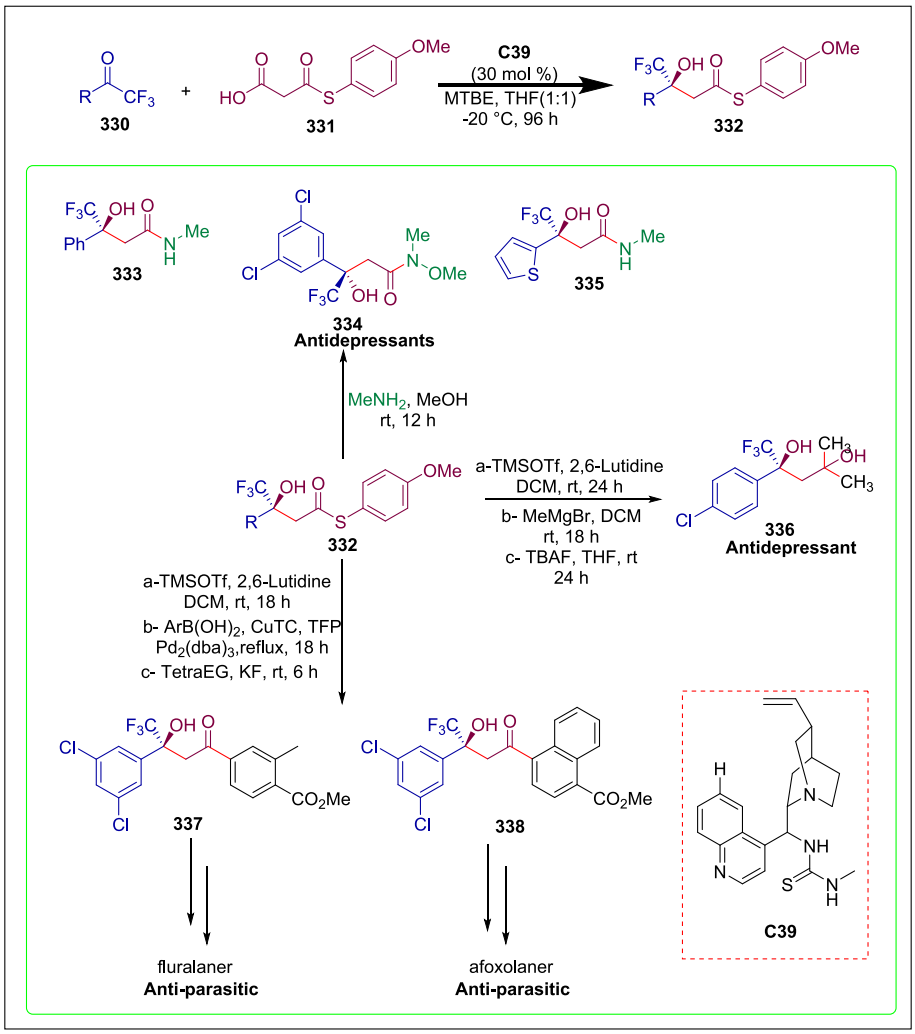
state, where it either donates an electron to an electrophile or accepts an electron from a nucleophile, initiating redox reactions like photocatalytic reductions, oxidations, or cycloadditions. These catalysts are important for sustainable and green chemistry because they are often very selective, adaptable to mild reaction conditions, and provide a metal-free and energy-efficient substitute for conventional photoredox systems. In this chapter, we described different photo-organocatalysts such as benzophenone and 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene photocatalyst for the synthesis of significant pharmaceutically potent molecules like anticancer, antioxidant and antibacterial compounds.

8. Integrate cutting edge research

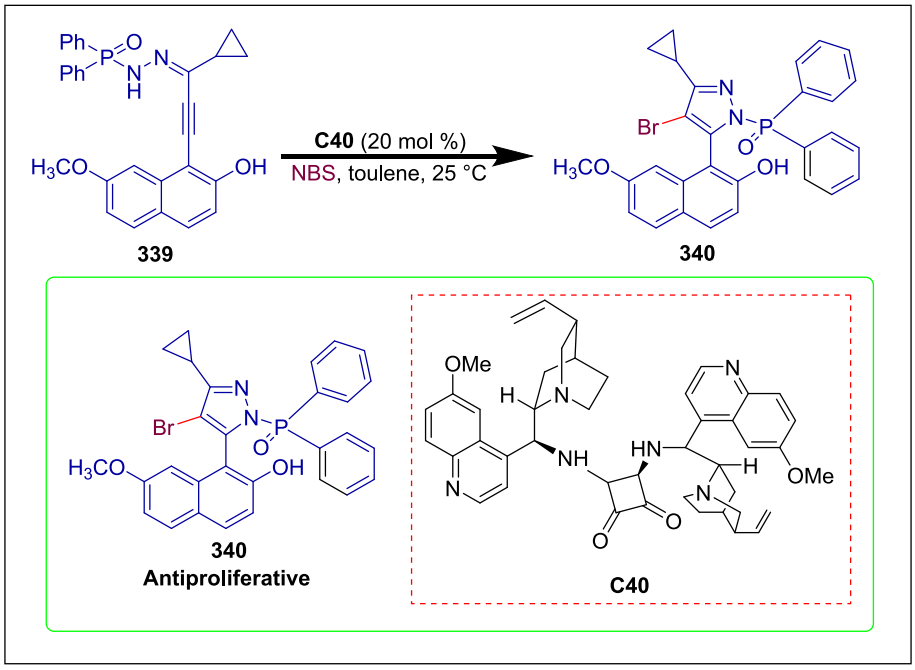
Advanced research in organocatalysis is pushing the boundaries of synthetic chemistry, with significant focus on enantioselective catalysis, sustainable practices, and novel reaction mechanisms. One of the most significant fields is the development of asymmetric organocatalysts that can perform highly selective, enantio-controlled reactions, important for producing complex drug moities. Scientists are currently investigating the concept of dual catalysis, which involves integrating metal or photoredox catalysis (Yao et al., 2022)with organocatalysis to provide novel



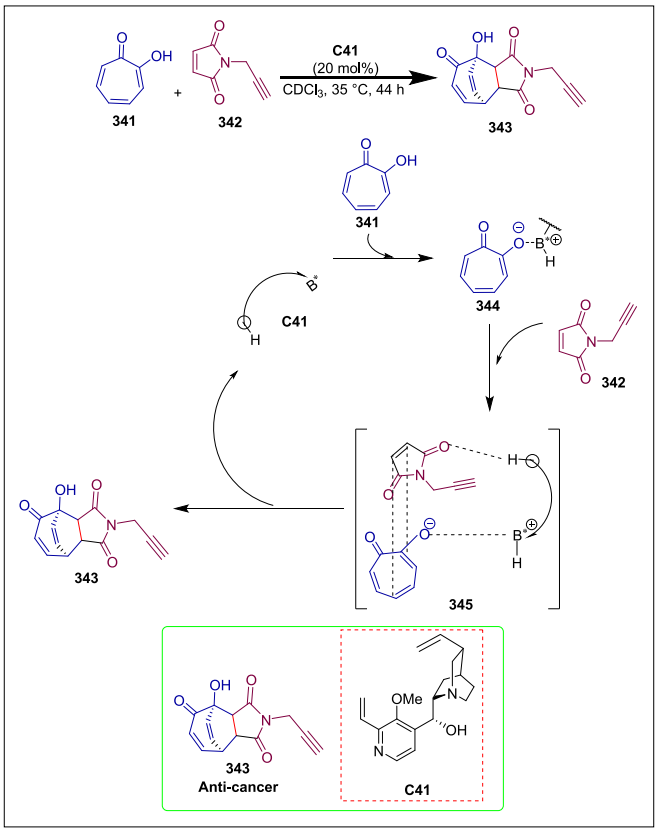
Scheme 47. Cinchona alkaloid catalyzed synthesis of spirooxindoles.



Scheme 48. CD-TU catalyzed synthesis of trifluoromethylated tertiary aldol pharmacophores.



Scheme 49. Cinchona alkaloids-derived squaramide catalyzed synthesis of naphthyl-pyrazole.



Scheme 50. Quinine catalysed synthesis of tropolones.

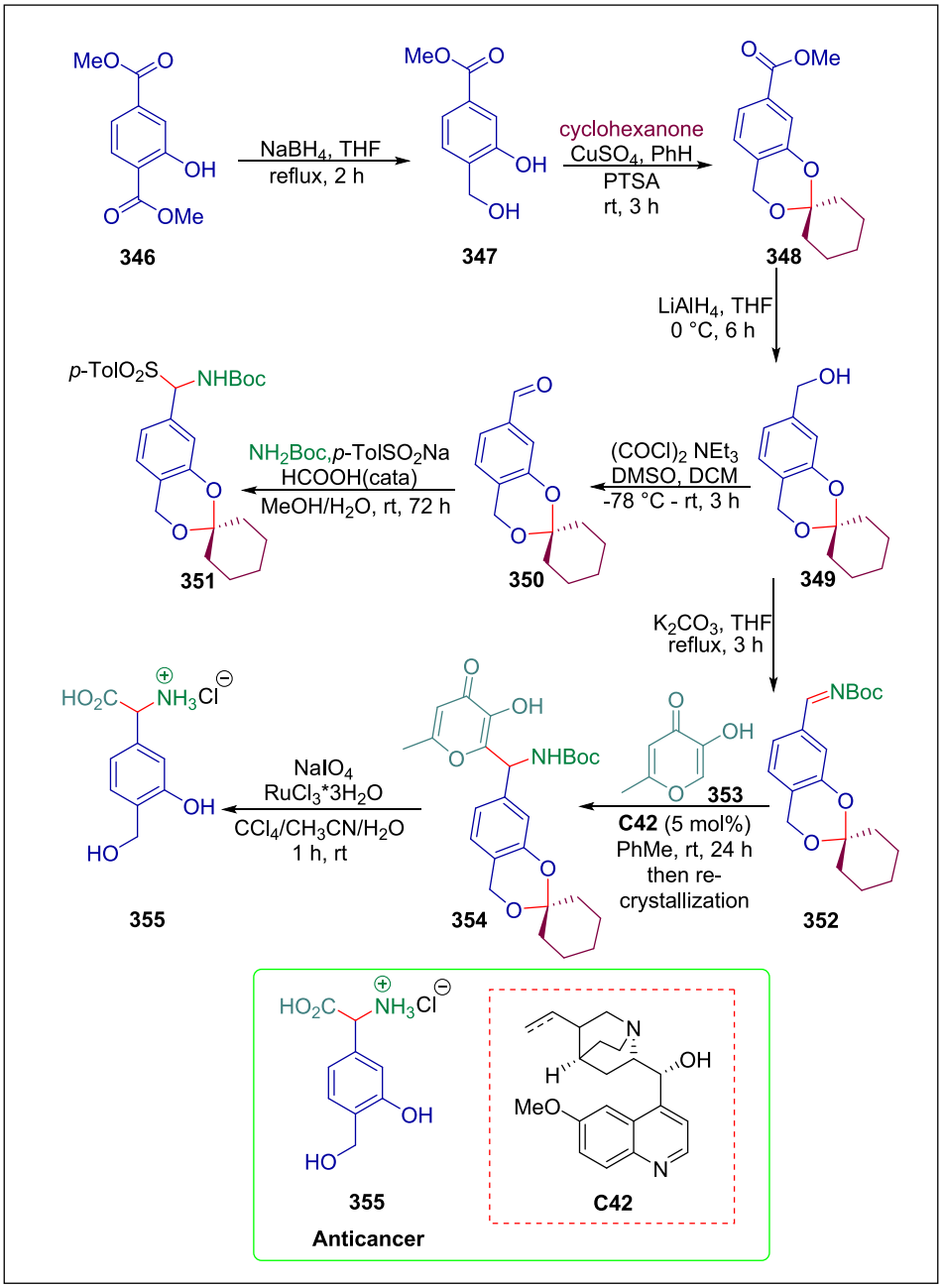
and effective reaction pathways in mild conditions. Deeper understanding of reaction pathways is being gained through computational research and mechanistic studies, which makes it possible to rationally design catalysts with higher efficiency. Sustainable developments include the synthesis of enzyme-like biomimetic catalysts that encourage extremely selective reactions in aqueous or environmentally benign conditions. Organocatalysis is also transforming the field of polymer research by enabling metal-free, organocatalytic polymerization for biodegradable materials (Zhou et al., 2022). Organocatalysts are also improving efficiency in cascade and multicomponent reactions (Grondal et al., 2010) by facilitating challenging molecular syntheses in fewer steps with less waste. These developments are making organocatalysis a more effective and sustainable tool in modern synthetic chemistry Fig. 7.

9. Conclusion

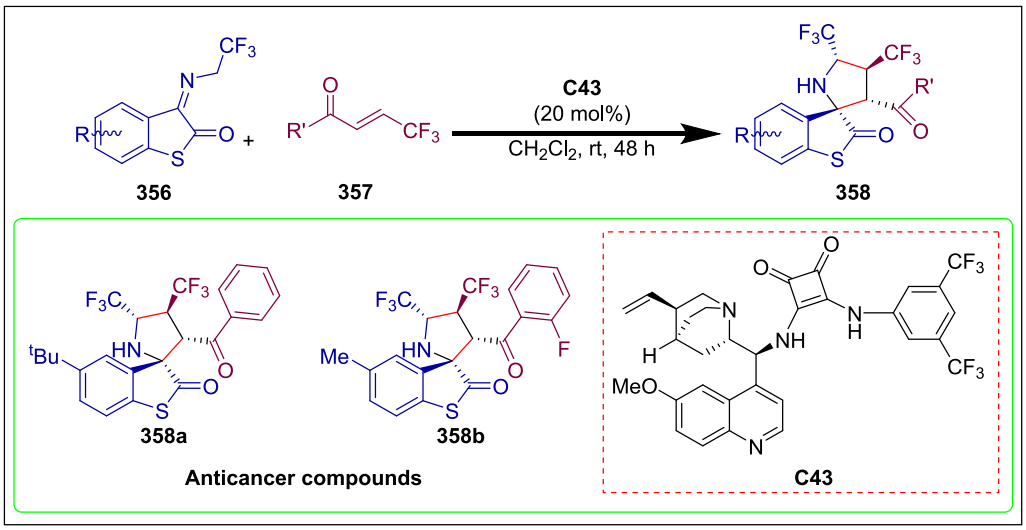
Organocatalysis has emerged as the third main technique for catalyzing a diverse range of chemical processes apart from enzymes and metal catalysis. It enables eco-friendly, metal-free synthesis of chiral drugs, fine chemicals, and biodegradable polymers, while also facilitating complex natural product construction. Due to its sustainability and recyclability, it is a vital tool in green chemistry. According to a green chemistry viewpoint, the formation of a highly stereoselective organocatalytic approach in an aqueous medium has become the most appealing topic of organic chemistry. The previous few years have seen phenomenal growth in this sector, and more reactions are anticipated in the future. This review describes the potential and versatility of organocatalyzed reactions in the field of synthetic organic chemistry. It explains the use of different cost-effective, and environment-friendly organocatalysts for the synthesis of many remarkable bioactive molecules. Organocatalysts are green catalysts due to their ability to facilitate reactions without the need for toxic metals, harsh conditions, or excessive waste. For example, proline, a naturally occurring amino acid, is utilized in aldol reactions and frequently works in ambient and aqueous environments. Its nontoxic and biodegradable nature makes it highly sustainable. N-Heterocyclic carbenes (NHCs) can be used with greener solvents because they don't require metal catalysts and can function in milder environments. Similarly, without the need of transition metals, chiral phosphoric acids facilitate enantioselective processes. Furthermore, thiourea catalysts, which are employed in hydrogen-bonding catalysis, facilitate reactions in green solvents and mild conditions, supporting environment friendly synthetic methods. Even with its benefits, organocatalysis cannot replace the importance of metal and biocatalysis. Certain significant reactions like cross-coupling and metathesis, which are catalyzed by transition metals, are still improbable to occur through organocatalysis. Because of their narrow range of substrates, lower reactivity, and sensitivity to environmental factors, organocatalysts can result in longer reaction times and lower yields. In addition, achieving high enantioselectivity can be challenging, and their mechanisms are often not well understood.Thus, further research into organocatalysis is necessary to create an extremely efficient catalyst that can perform several reactions with improved practical applications.

CRediT authorship contribution statement

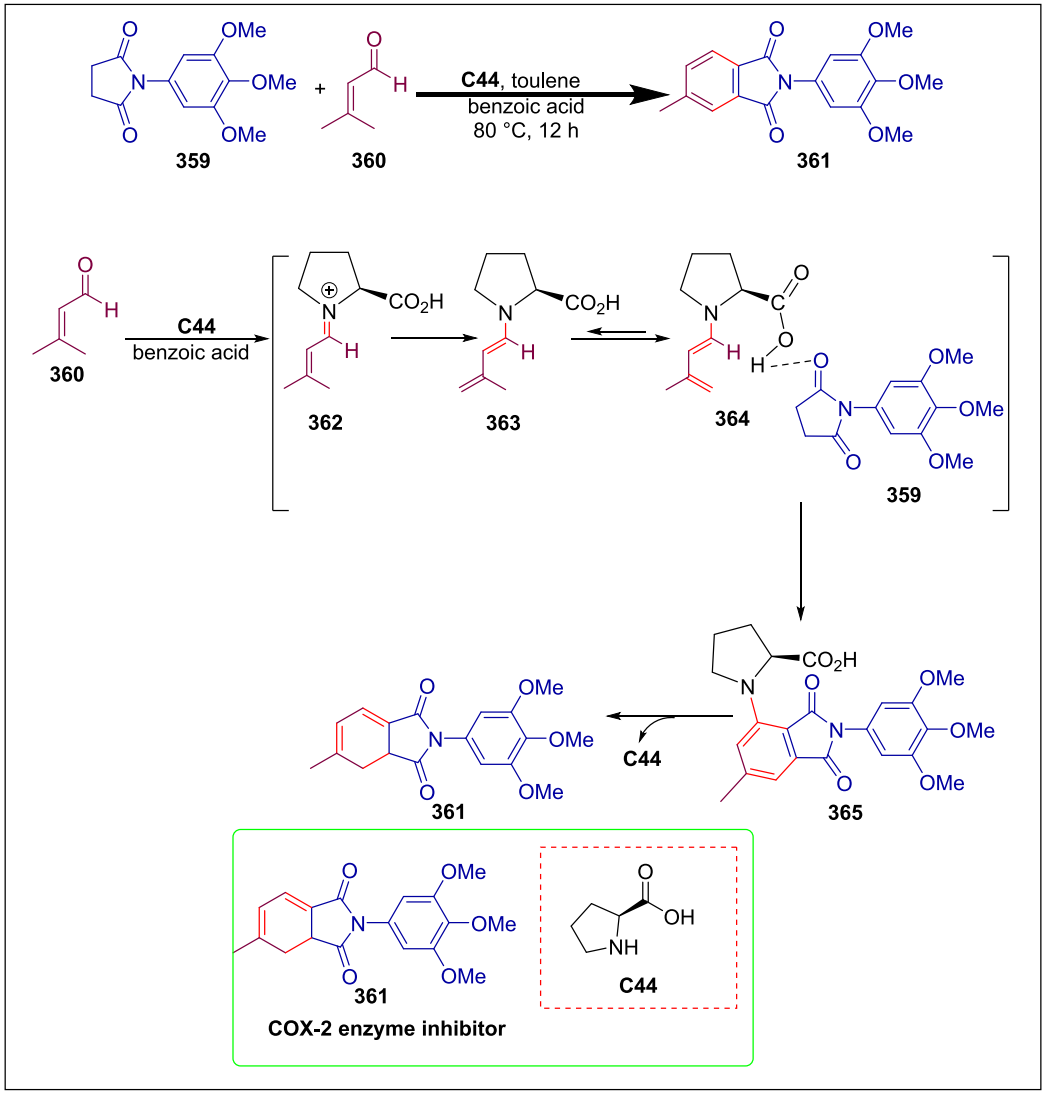
Labiqa Aman: Writing – review & editing, Writing – original draft. **Shehla Khalid:** Writing – review & editing, Visualization, Conceptualization. **Nasir Rasool:** Supervision, Funding acquisition. **Almeera Zia:** Visualization, Software. **Muhammad Imran:** Visualization, Project



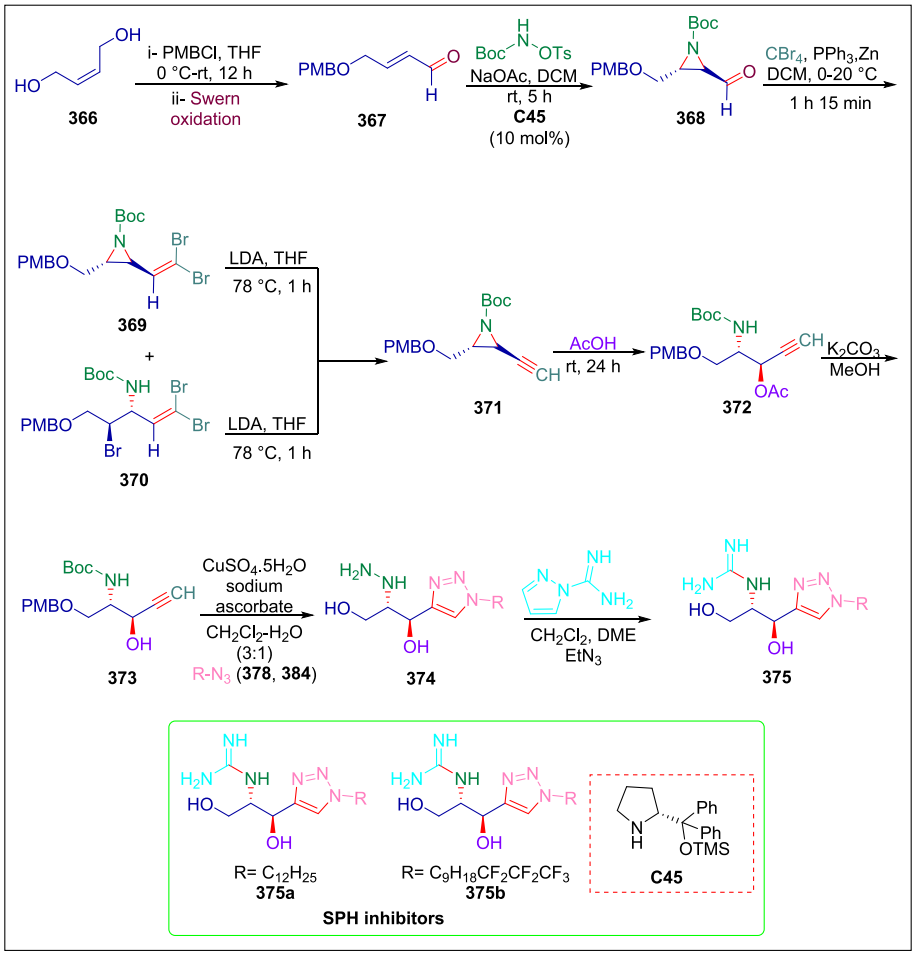
Scheme 51. Hydroquinine-catalyzed synthesis of (*S*)-forphenicinol hydrochloride.



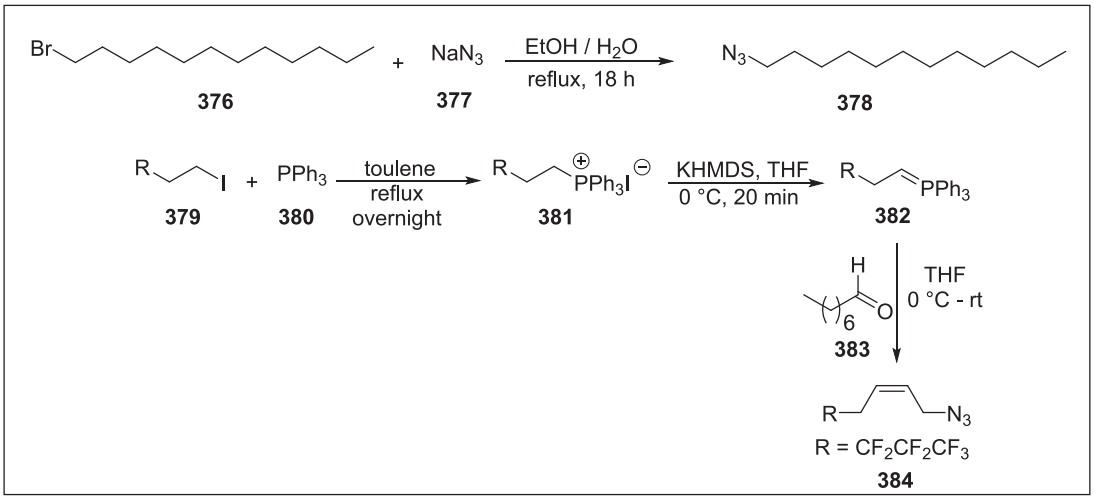
Scheme 52. Quinine-derived squaramide catalyzed synthesis of spiro pyrrolidine-benzothiophenones.



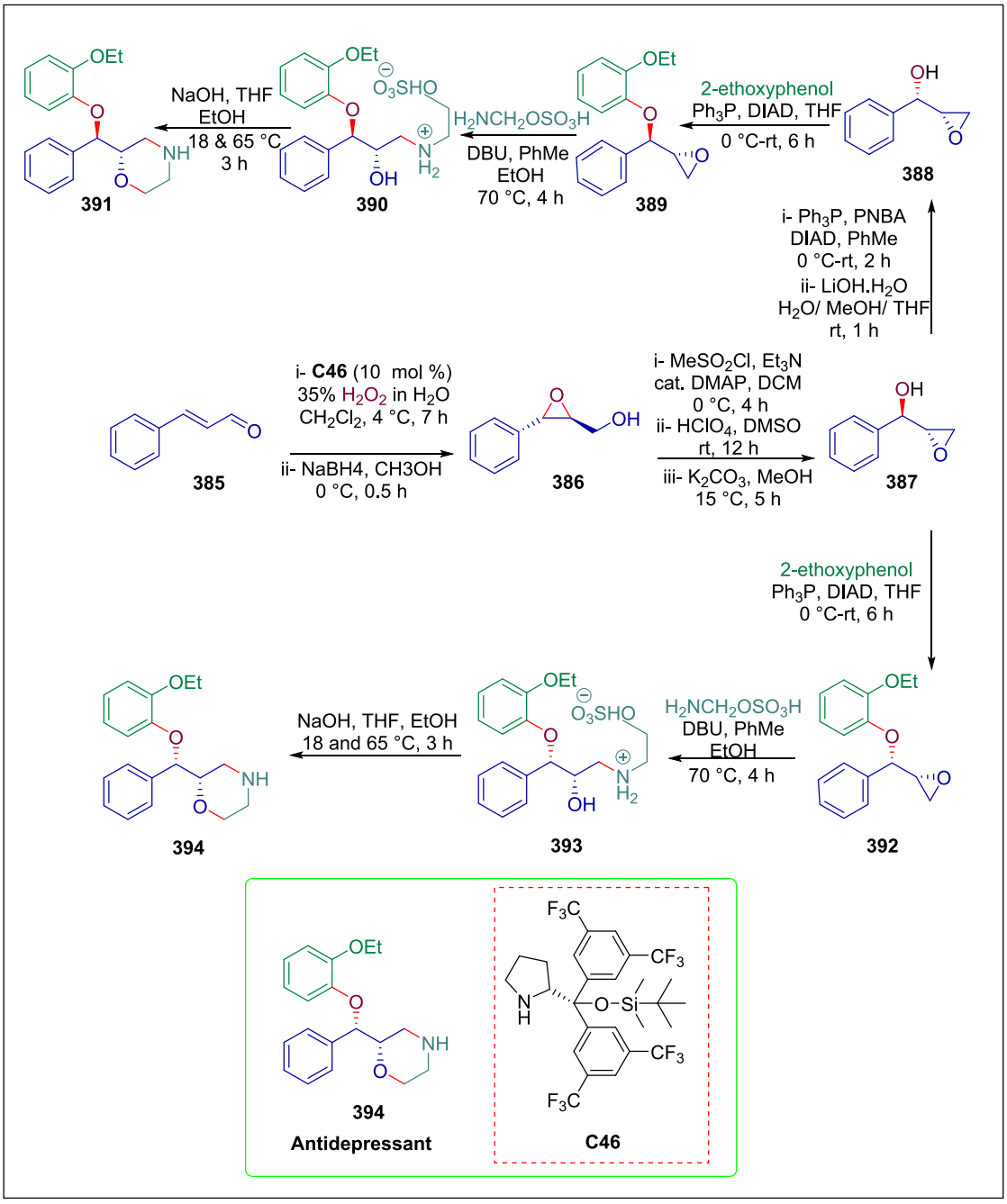
Scheme 53. Proline catalyzed synthesis of phthalimides.



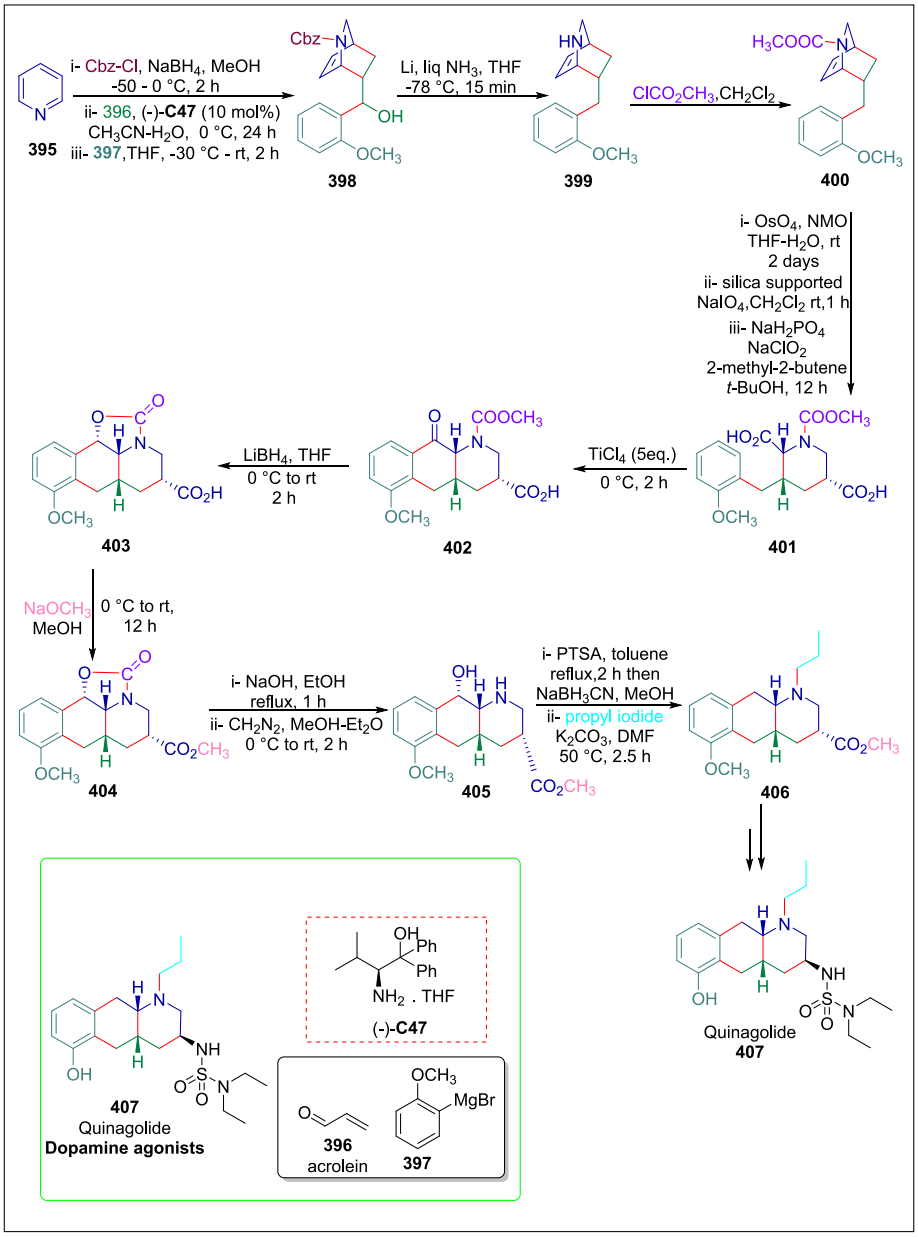
Scheme 54. Prolinol catalyzed synthesis of sphingosine analogues.



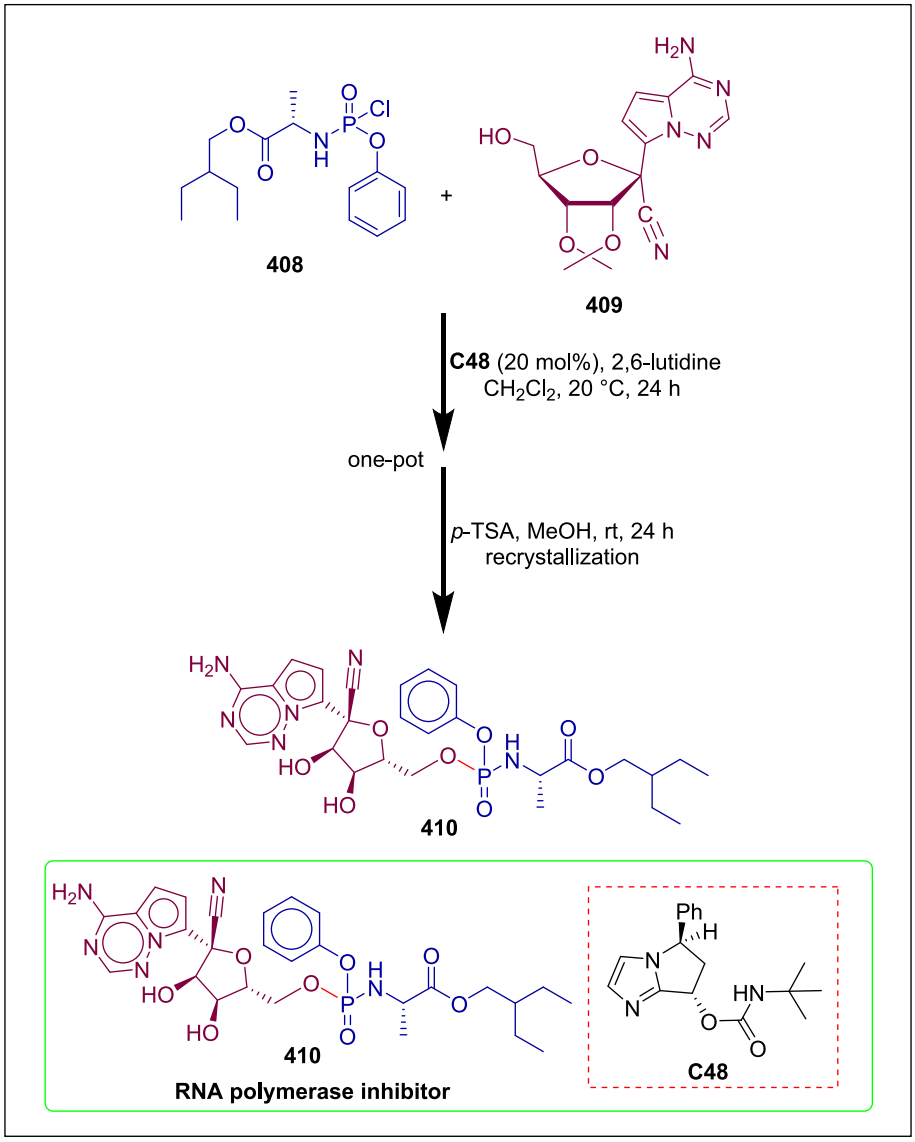
Scheme 55. Synthesis of azides.



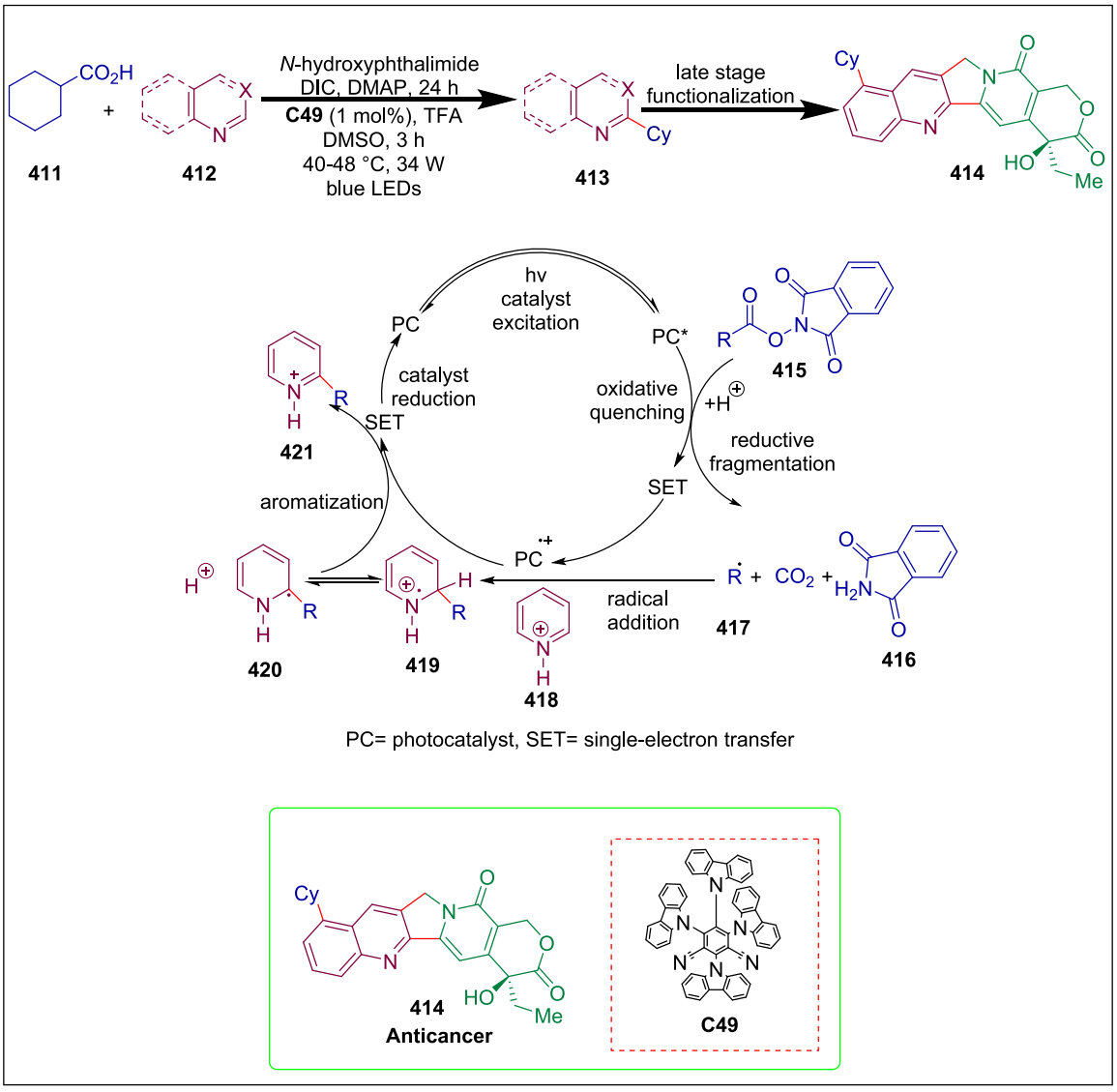
Scheme 56. Prolinol catalyzed synthesis of reboxetine.



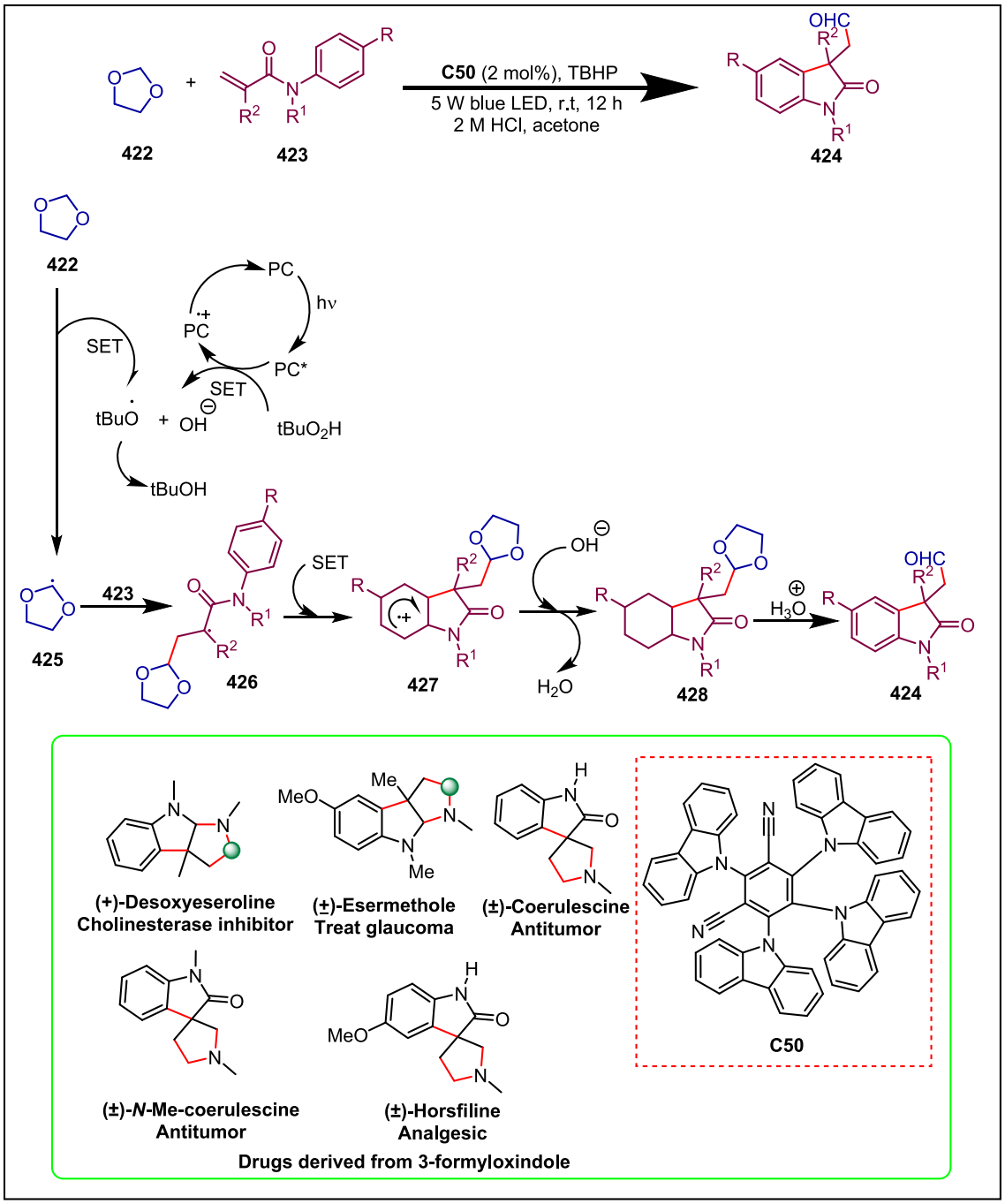
Scheme 57. β −amino alcohol catalyzed synthesis of Quinagolide.



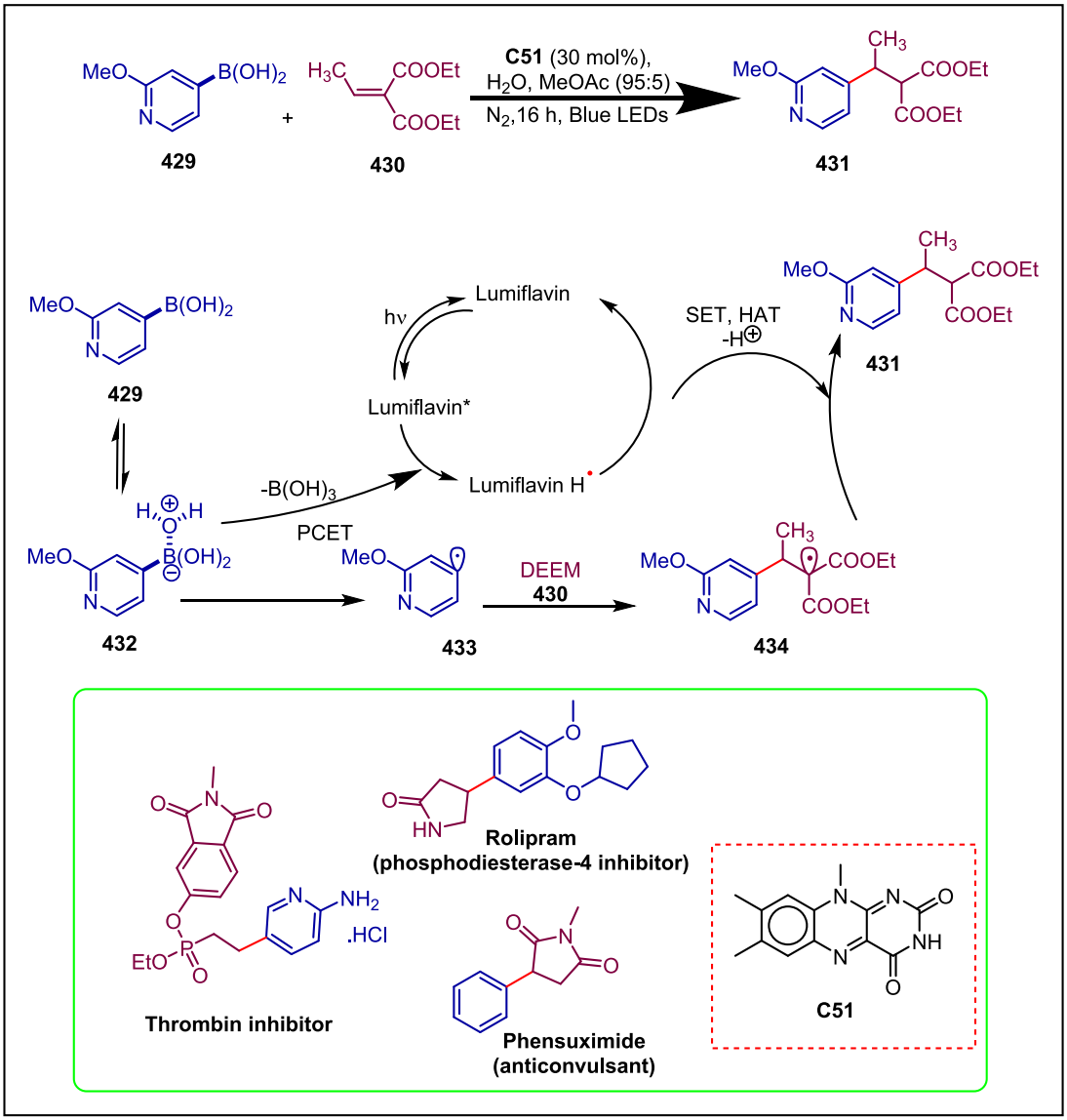
Scheme 58. Chiral carbamate catalyzed synthesis of remdesivir.



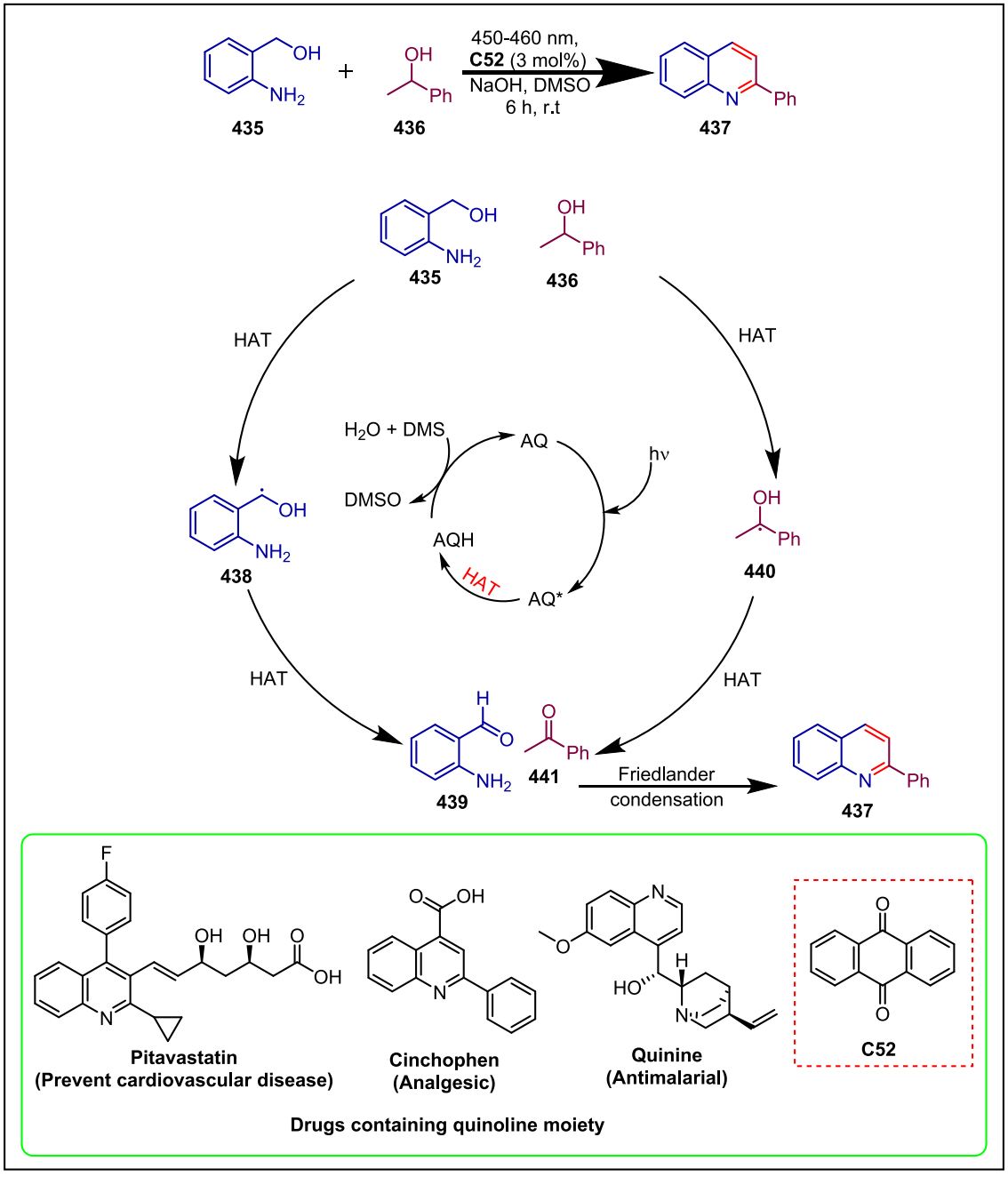
Scheme 59. Organo-photocatalyzed synthesis of cyclohexyl quinolines.



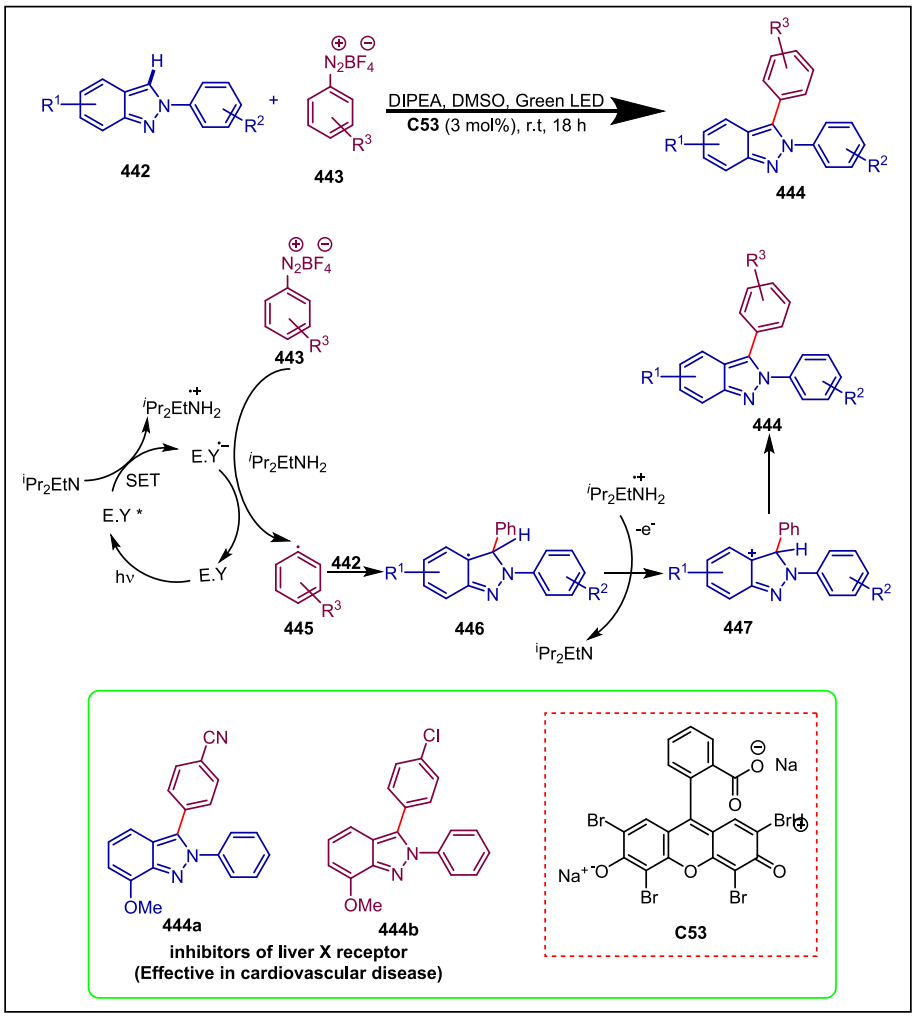
Scheme 60. CC-CMP catalyzed synthesis of 3-formyloxindoles.



Scheme 61. Lumiflavin catalysed synthesis of alkylated products.



Scheme 62. Anthraquinone catalyzed synthesis of quinolines.



Scheme 63. Eosin Y catalyzed synthesis of liver X-receptor inhibitor drugs.

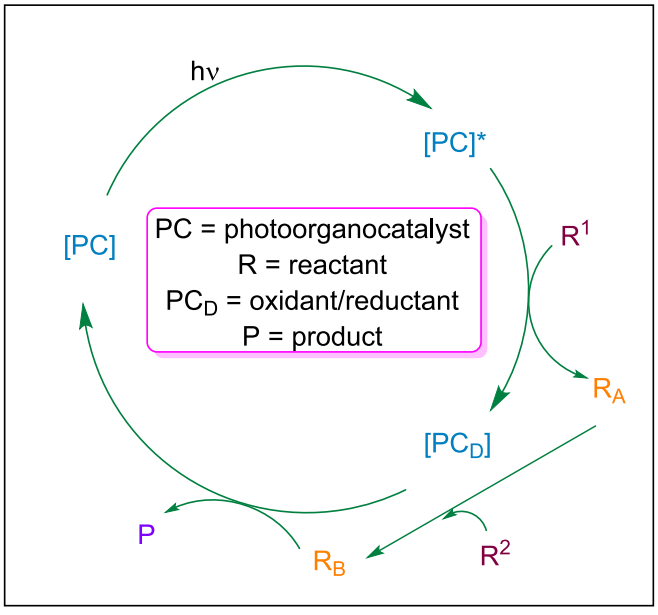


Fig. 6. Mechanism of photo-organocatalysis.

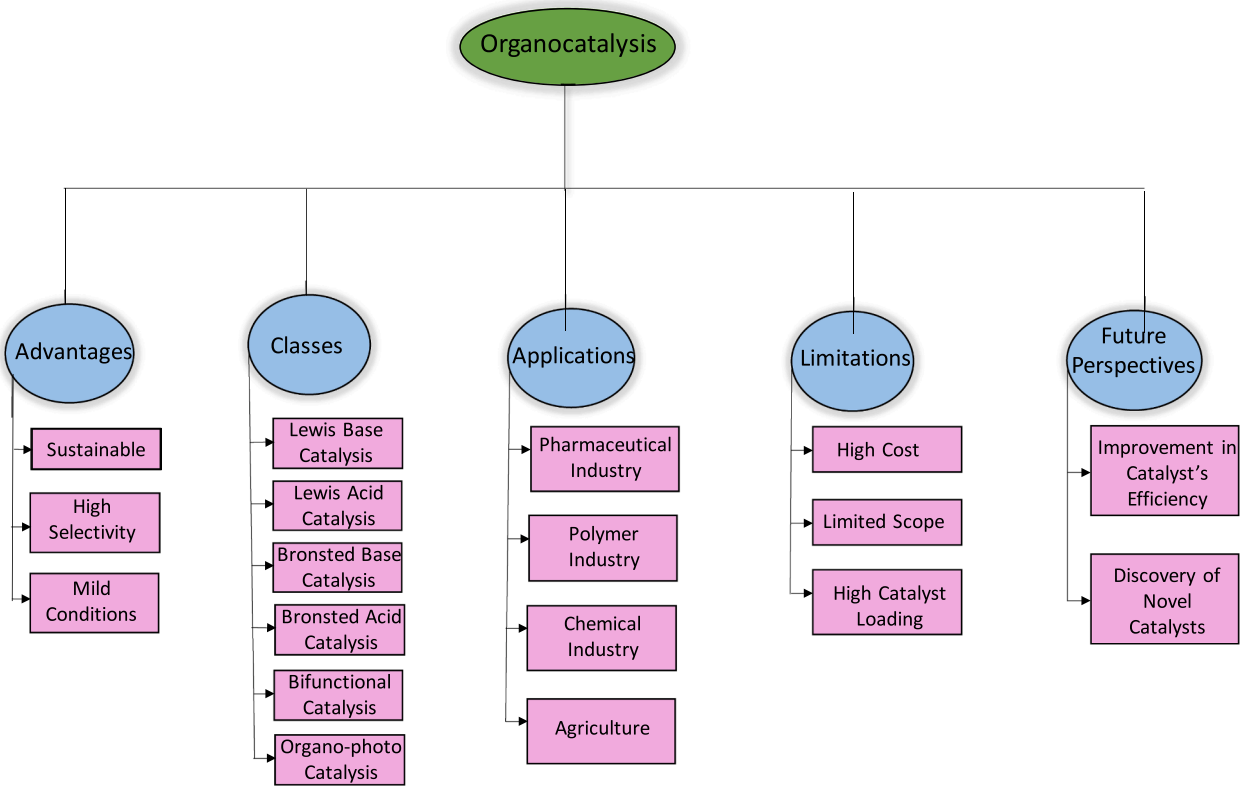


Fig. 7. Flow chart outlining the main points of this review.

administration. **Marius Irimie:** Writing – review & editing. **Codrut Ioan Ciurea:** Visualization, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2024.106027.

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