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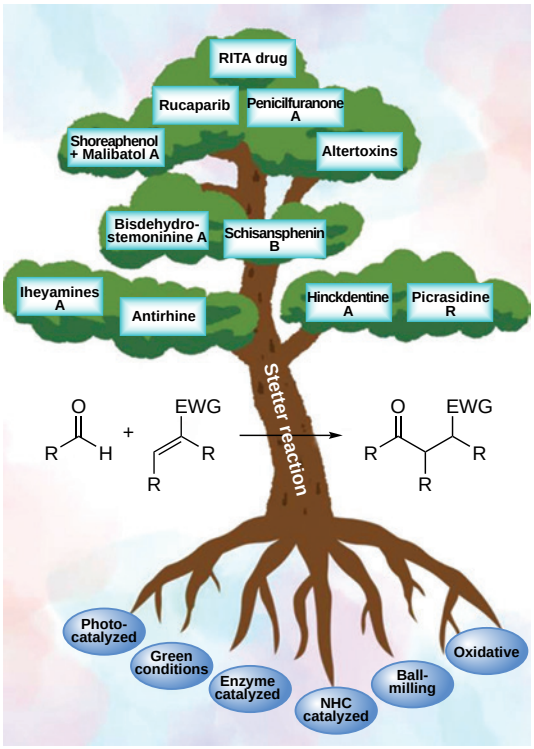
The Stetter reaction: modern methodologies and useful applications in total synthesis of natural products and drugs

Ayesha Nawaz, Ameer Fawad Zahoor*

Department of Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan

The Stetter reaction, a powerful umpolung strategy using the catalysis with nucleophilic carbenes, enables the formation of 1,4-dicarbonyl compounds through the conjugate addition of aldehydes to Michael acceptors. Since its discovery in the 1970s, this reaction has evolved through thiazolium, triazolium, and many more catalysts, and more recently, with chiral *N*-heterocyclic carbenes for asymmetric applications. This review discusses modern advances in the Stetter reaction under green conditions, enzyme catalysis, photochemical activation, and ball-milling techniques. It integrates recent advances in green chemistry, solvent-free systems, and biocatalytic processes while correlating them with applications in the total synthesis of natural products and pharmaceuticals. Particular focus is placed on the evolution of chiral NHCs, artificial Stetterases, and photoinduced pathways, which expand the reaction's utility in asymmetric and sustainable syntheses. These methodologies highlight the reaction's versatility in constructing complex compounds, its environmental compatibility *via* aqueous or solvent-free conditions, and its ever-growing role in medicinal chemistry. The bibliography includes 140 references.

Keywords: Stetter reaction, asymmetric Stetter reaction, Stetter-type reaction, Breslow intermediate, natural products synthesis.



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1. Introduction

Name reactions are well-known chemical transformations named after their discoverers; they are important because they simplify complex syntheses and save time by providing proven, predictable reaction pathways.[1–3] The Stetter reaction is an umpolung (polarity inversion) reaction between an aldehyde and α,β-unsaturated compound yielding 1,4-addition products, catalyzed by a nucleophilic catalyst. In 1973, Stetter and Schreckenberg[4] first described the umpolung process catalyzed by cyanide ions, which involved the reaction of aldehydes with Michael acceptors such as α,β-unsaturated ketones, esters, nitro compounds, and nitriles. In 1976, Stetter synthesized 1,4-dicarbonyl products through thiazolium-catalyzed reactions between aldehydes and Michael acceptors. Later, this reaction was named in his honor — the 'Stetter reaction'. The thiazolium-catalyzed approach covers a variety of aromatic and aliphatic aldehydes **1** with Michael acceptors **2** to produce 1,4-addition products **3** with high selectivity (Scheme 1).[5,6] A wide variety of substrates, including diversely substituted benzoins, α,β-unsaturated esters, various aldehydes, including aliphatic,

A.Nawaz. M.Phil. in Organic Chemistry, Department of Chemistry, Government College University Faisalabad, Pakistan.
E-mail: nawazayesha638@gmail.com
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A.F.Zahoor. PhD in Chemistry, Professor at the Department of Chemistry, Government College University Faisalabad, Pakistan.
E-mail: fawad.zahoor@gcuf.edu.pk

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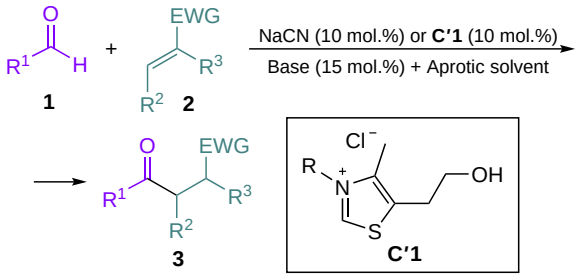
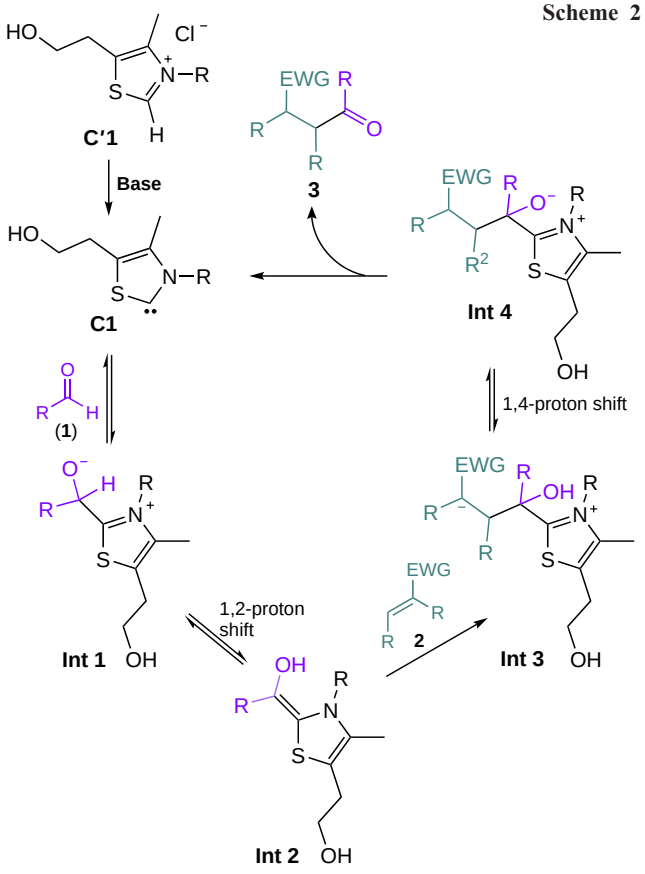
Scheme 1



aromatic and heteroaromatic, ketones, nitriles, and nitro derivatives can all be utilized as appropriate Michael acceptors in the Stetter reaction.[7–10] A wide range of *N*-heterocyclic carbene (NHC)-based catalysts, *e.g.*, thiazolium, triazolium and imidazolium carbenes are often effective catalysts to umpolung the aldehydes in the Stetter reaction.[11–13]

An acceptable mechanism for the Stetter reaction includes deprotonation of the thiazolium salt **C′1** with the base followed by it conversion into the free carbene **C1**. Thiazolium carbene **C1** reacts with an aldehyde 1 to give a tetrahedral intermediate **Int 1**, which transforms into nucleophilic Breslow intermediate **Int 2** (enaminol) by 1,2-proton shift.[14] In 1958, Ronald Breslow[14] first proposed the intermediates produced in all thiamine-catalyzing reactions. Breslow intermediate **Int 2** undergoes an irreversible addition to the Michael acceptor to generate intermediate **Int 3**, which converts into intermediate **Int 4** by 1,4-proton shift, and then, after the release of free carbene **C1**, provides 1,4-dicarbonyl compound **3** (Scheme 2) or other derivatives like nitro-ketones,[10] ketophosphonates,[15] or keto-nitriles.[16] Alternative approaches included aza-Stetter

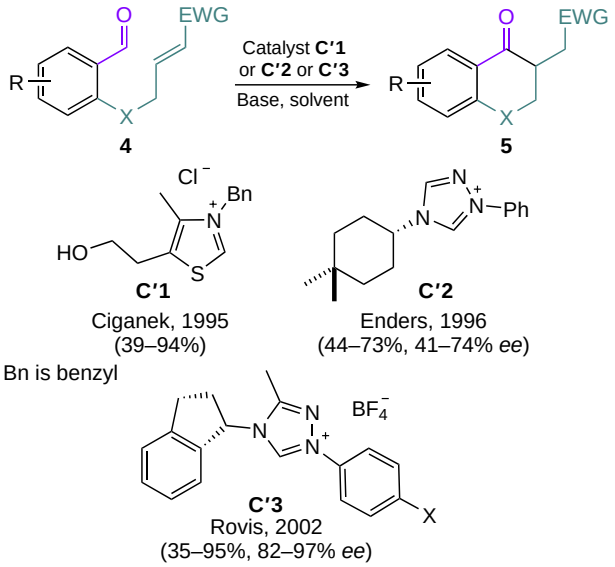
Scheme 2



reaction, producing aza-Breslow intermediate by imine umpolung[17] or sila-Stetter reaction, producing Breslow intermediate from acylsilanes.[7]

In 1995, Ciganek[18] reported the first intramolecular Stetter reaction. The first enantioselective intramolecular Stetter reaction was explained by Enders *et al.*[19] Later, enantioselective 1,4-bifunctional compounds were synthesized by asymmetric transformation using chiral NHCs as a catalyst. In 2002, Rovis and co-workers[20] prepared the most effective aminoindanol-substituted chiral triazolium NHC precatalyst for the enantioselective intramolecular Stetter reaction using amino indanol (Scheme 3).

Scheme 3

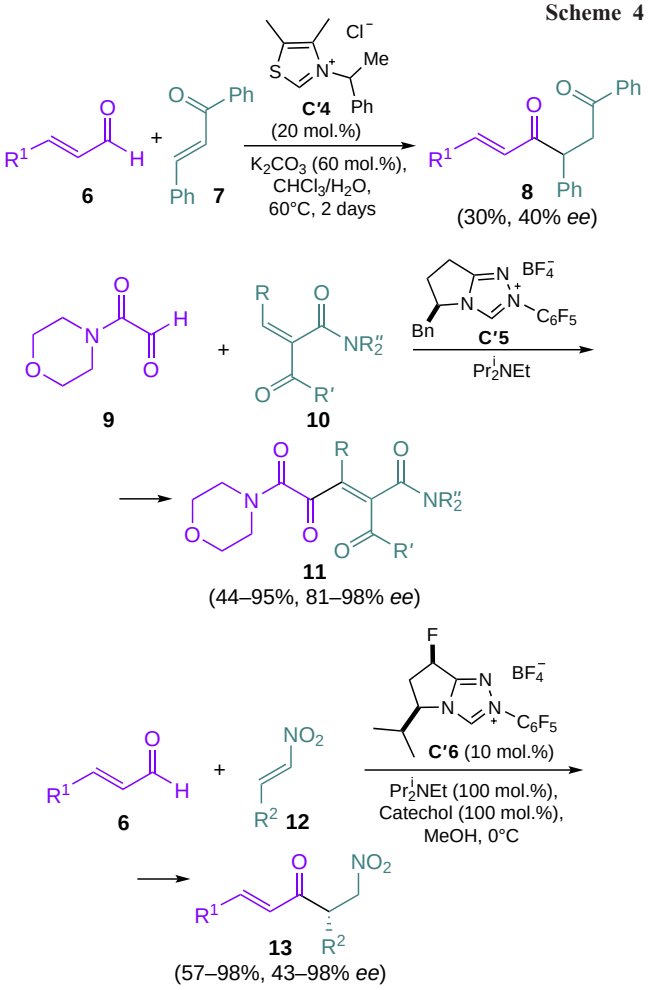


In addition, Enders *et al.*[21] carried out the first intermolecular Stetter reaction between α,β-unsaturated aldehydes and chalcones, using a chiral thiazolium salt **C′4** as a catalyst. Liu and Rovis[22] contributed to the asymmetric intermolecular Stetter reaction using glyoxamide moieties as an aldehyde component and alkylidene molecules as Michael acceptors. DiRocco and Rovis[23] used a fluorinated triazolium salt as a catalyst in the intermolecular Stetter reaction between β-nitroarene as a Michael acceptor and α,β-unsaturated aldehyde (Scheme 4).

The synthesis of natural products is very important because it provides an access to valuable bioactive compounds that are difficult to obtain from nature.[24–26] It also helps in developing new biological active compounds[27–29] and understanding complex biological processes. Synthetically essential 1,4-di-carbonyl compounds and their derivatives are produced by the Stetter reaction making it a versatile, adaptable, practical, and efficient method for synthesizing complex chemical compounds, including natural products like *trans*-sabiene hydrate **14**,[30] dihydrojasmone **15**, *cis*-jasmone **16**,[31] and (+)-monomorine I **17**,[32] hirsutic acid C **18**,[33] (–)-vallesamidine **19**,[34] and englerin A **20**,[35] as well as non-natural products like atorvastatin **21**[36] and haloperidol **22**[37] with potential medical applications. The Stetter reaction was also used to obtain the 1,4-diketone, intermediate compound in the synthesis of the product marketed under the brand name Lipitor (atorvastatin), and this modification was applied at the industrial level.[36,38]

In 2020, Heravi *et al.*[39] reviewed advancements in the Stetter reaction and its applications in the synthesis of natural products and heterocyclic compounds. In 2022, Shneine *et al.*[40] discussed

Scheme 4



different developments in the Stetter reaction. To date, many advancements have been reported concerning the Stetter reaction. This review covers recent (2020–2025) methodological approaches and syntheses of natural products and drugs *via* the Stetter reaction and offers an in-depth discussion of the Stetter reaction from both a mechanistic and practical perspectives. While earlier reviews mainly focused on classical NHC-catalyzed versions or specific reaction types, herein, organocatalytic, enzymatic, photochemical, and mechano-chemical approaches to the Stetter reaction are summarized. In addition, traditional solvent-based methods with emerging green and sustainable protocols, highlighting their relative advantages and limitations are compared. Furthermore, the industrial relevance and future potential of the Stetter reaction are emphasized, providing a clearer view of how this transformation can be adapted for large-scale and environmentally friendly chemical syntheses.

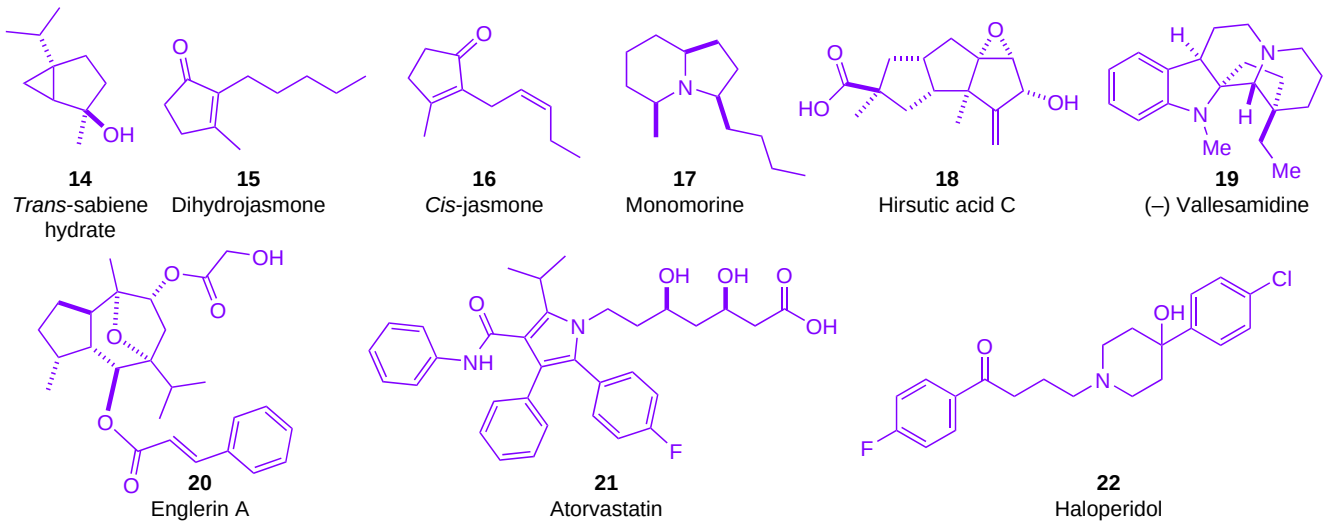
2. Methodological approach

2.1. Green conditions for the Stetter reaction

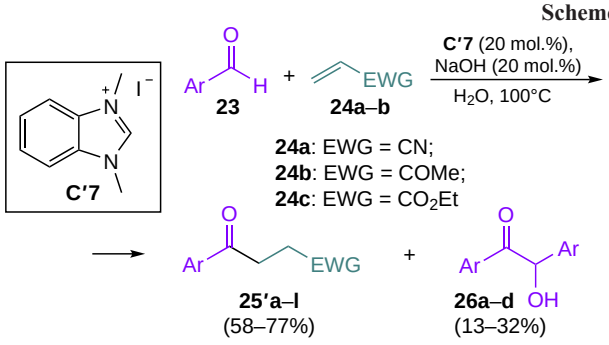
Green chemistry focuses on designing chemical processes that reduce waste and minimize the use of hazardous substances. It promotes safer, energy-efficient, and environmentally friendly methods for producing useful compounds.[41] In 2022, Phungpis and Worawut[42] reported a novel 'green' modification of an intermolecular Stetter reaction efficiently between aromatic aldehydes **23** and acrylonitrile/methyl vinyl ketone/ethyl acrylate **24** in the presence of NaOH and the greenest solvent (water) at 100°C catalyzed by *N*,*N*-dimethylbenzimidazolium iodide **C′7** (Scheme 5). Under optimal conditions, reactions between aldehydes **23** and α,β-unsaturated compounds **24a**,**b** produced 1,4-addition products **25a–f**,**j′**,**k′** in 70–77% along with minor acyloin derivatives **26a–d** as by-products. But with a less electrophilic double bond in ethyl acrylate **24c**, the Breslow intermediate reacted more readily with more reactive aldehydes **23**, despite ethyl acrylate **24**, which produced high yields of acyloin derivatives **26a–d** and moderate yields of 1,4-addition products **25g–i**,**l′** (58–66%).

According to the proposed mechanism of the Stetter reaction, NaOH deprotonates *N*,*N*-dimethylbenzimidazolium iodide **C′7** to yield carbene **C7**, which then reacts with aldehyde **23** to produce the intermediate **Int 5**, as previously suggested (Scheme 6).[43] After 1,2-proton transfer, intermediate **Int 5** transforms into Breslow intermediate **Int 6**. Then, intermediate **Int 6** nucleophilically attacks Michael acceptors **24** to produce the tetrahedral intermediate **Int 7**. The water-mediated 1,4-proton transfer degenerates the tetrahedral intermediate **Int 7** to intermediate **Int 8**, which then gives 1,4-addition products **25a–l** and leads to regeneration of the carbene catalyst **C7**. The use of NaOH provides useful benefits including high basicity, reusability, and simple separation from the products.

Structures 14–22



Scheme 5



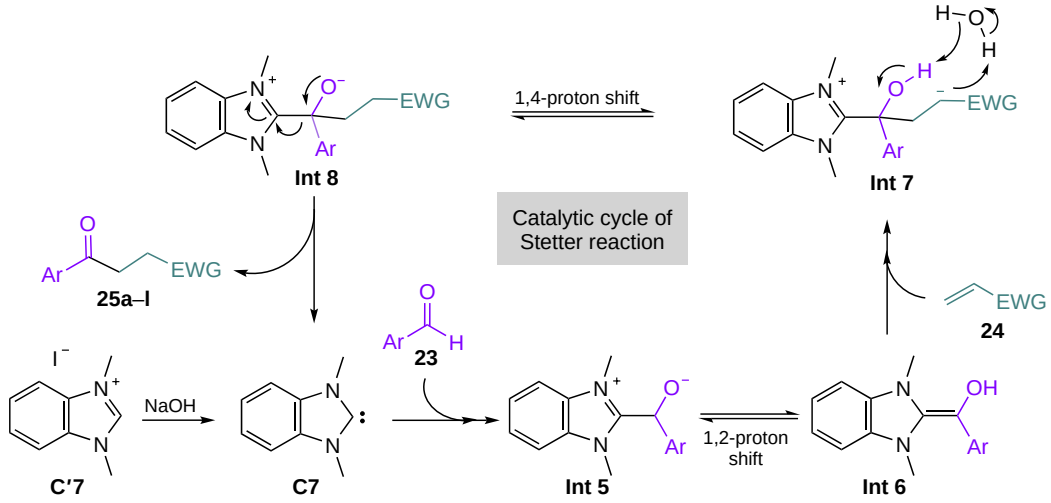
25a: Ar = Ph, EWG = CN (75%);
25b: Ar = 4-ClC_6H_4, EWG = CN (77%);
25c: Ar = 4-MeC_6H_4, EWG = CN (71%);
25d: Ar = Ph, EWG = COMe (73%);
25e: Ar = 4-ClC_6H_4, EWG = COMe (75%);
25f: Ar = 4-MeC_6H_4, EWG = COMe (70%);
25g: Ar = Ph, EWG = CO_2Et (62%);
25h: Ar = 4-ClC_6H_4, EWG = CO_2Et (66%);
25i: Ar = 4-MeC_6H_4, EWG = CO_2Et (58%);
25j′: Ar = C_5H_4N, EWG = CN (73%);
25k′: Ar = C_5H_4N, EWG = COMe (72%);
25l′: Ar = C_5H_4N, EWG = CO_2Et (64%)

26a: Ar = Ph;
26b: Ar = 4-ClC_6H_4;
26c: Ar = 4-MeC_6H_4;
26d: Ar = 4-C_5H_4N

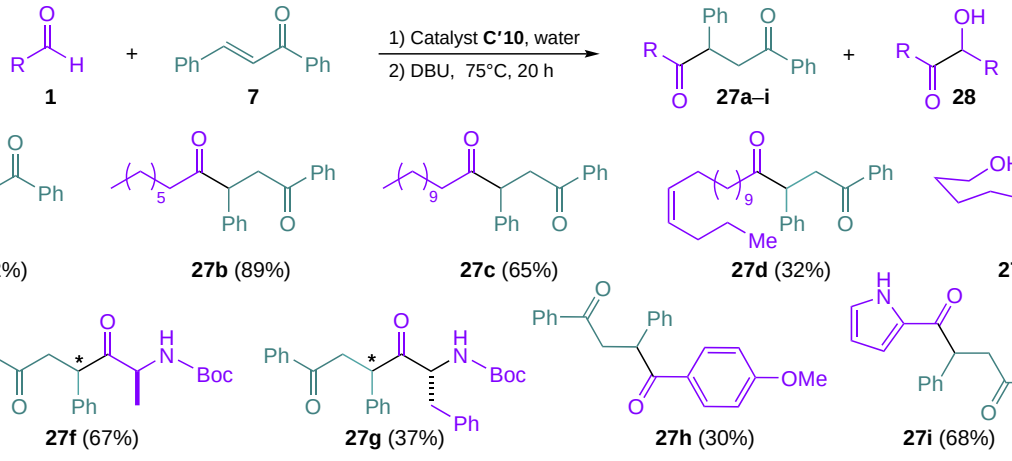
Furthermore, with a constant yield of 65%, the benzimidazolium salt and NaOH may be employed in at least four more reactions. An efficient and environmentally friendly method for synthesizing 1,4-addition products by the Stetter reaction showcases the potential for practical applications in organic synthesis. The use of water as a solvent and the ability to recycle the catalyst align with principles of green chemistry, emphasizing sustainability in chemical processes.

In 2020, Debiais *et al.*[44] reported the first bio-inspired NHC-catalyzed Stetter reaction between aldehyde **1** and chalcone **7** in water, which imitated the thiamine diphosphate (vitamin B1) cofactor essential for biochemical processes. The authors analyzed the Stetter reaction, catalyzed by thiazolium salts **C′1**, **C′8**–**C′12** as thiamine analogues, and revealed that water promoted the formation of benzoin as a side product compared to reactions carried out in an organic solvent (THF). The Stetter reaction catalyzed by thiazolium salt **C′10** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and water at 75°C for 20 h, exhibited the highest efficiency, achieving 30–90% conversion mainly of the 1,4-diketone products **27a**–**i** (Scheme 7). The substrate scope of the reaction was successfully extended to various aldehydes, and the effect of solvent and temperature on product selectivity was investigated. Lower temperatures are more appropriate for biomolecule compatibility; however, higher temperatures speed up the process. These findings inspired the synthesis of more lipophilic thiazolium salts **C′11** and **C′12**; their efficiency was compared with that of salt **C′10**. Catalyst **C′10** demonstrated the highest performance, achieving conversion up to 90% in water at 75°C, indicating excellent catalytic efficiency under aqueous conditions. In contrast, catalysts **C′11** and **C′12** showed moderate to lower activities. Overall, catalyst **C′8** significantly outperformed the

Scheme 6



Scheme 7

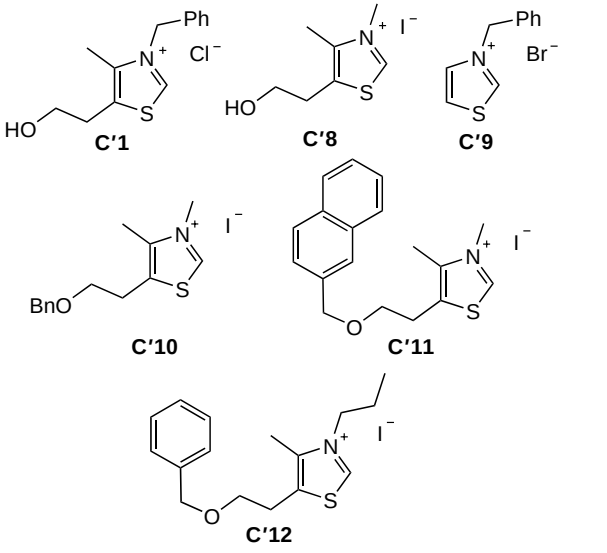


27a (72%) **27b** (89%) **27c** (65%) **27d** (32%) **27e** (70%)

27f (67%) **27g** (37%) **27h** (30%) **27i** (68%)

Boc is *tert*-butoxycarbonyl

Structures C′1, C′8–C′12

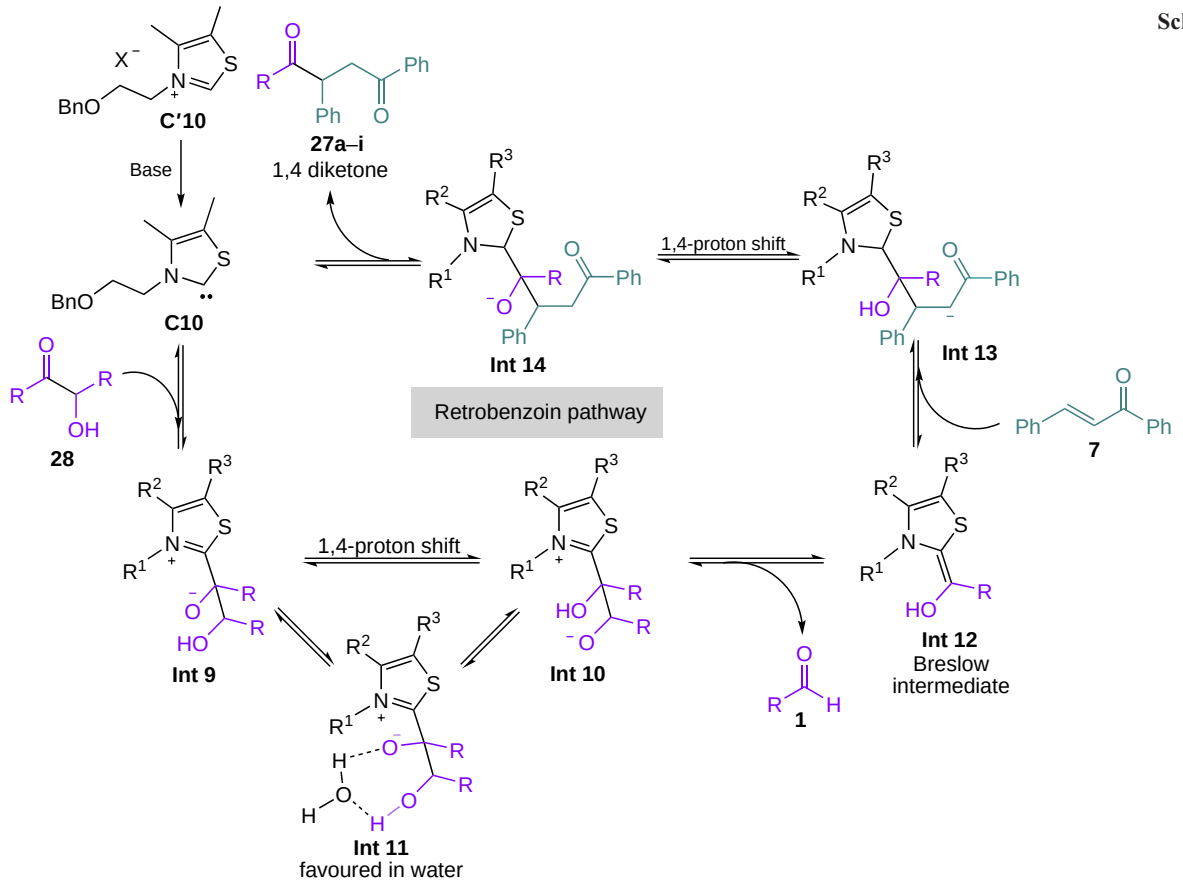


other ones making it the most effective for the bio-inspired NHC-catalyzed Stetter reaction in aqueous media.

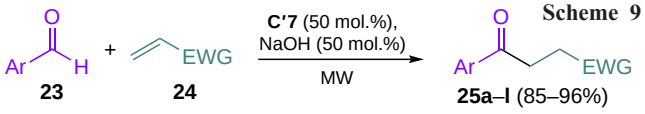
The reaction is initiated by the deprotonation of precatalyst thiazolium salt **C′10** to form the reactive NHC catalyst **C10**, which then reacts with benzoin **28** to yield the intermediate **Int 9** (Scheme 8). Then, intermediate **Int 9** is converted into intermediate **Int 10** by the 1,4-proton shift promoted by H_2O shown in intermediate **Int 11**. After that, intermediate **Int 11** eliminates aldehyde **1** to give the Breslow intermediate **Int 12**, which nucleophically reacts with Michael acceptor **7** to give intermediate **Int 13**. The intermediate **Int 13** transforms into intermediate **Int 14** *via* the 1,4-proton shift and finally affords the 1,4-addition product **27a–i**, regenerating catalyst **C10**. According to the study, although Breslow intermediates were generated more rapidly in water, the rate-limiting step shifted from proton transfer to the retrobenzoin reaction, thereby reducing overall kinetics. To examine this effect, benzoin was used as a masked aldehyde, and the retrobenzoin route was found to be realized slower in water due to the formation of H-bonded solvated species (see Scheme 8). The reaction in water produced a heterogeneous emulsion, indicating a catalytic mechanism in which the formation of hydrophobic droplets affected reactivity. The efficiency of the process was depended on this environment, which shielded important Breslow intermediates confined in hydrophobic pockets of enzymes. The study aligns with green chemistry principles by demonstrating an organocatalytic reaction in water, thereby reducing the use of harmful solvents. It provided valuable mechanistic insights, optimizing efficiency and expanding the reaction scope for biomolecules and synthetic applications. The findings laid the groundwork for future research in the development of catalysts and bioconjugation techniques. While aqueous media are eco-friendly, solubility issues and complex pathways hamper optimization, especially at lower temperatures. Further research is needed to enhance catalyst performance, broaden the substrate scope, and improve industrial scalability.

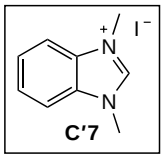
In 2024, Phungpis *et al.*[45] reported an intermolecular Stetter reaction between aromatic aldehydes **23** and α,β-unsaturated compounds **24** catalyzed by *N*,*N*-dimethylbenzimidazolium iodide catalyst **C′7** under microwave irradiation (MW) (Scheme 9). In the absence of an organic solvent, the reaction produced the desired products **25a–l** in excellent yields (85–96%). These results were compared with the yields of 1,4-addition products **25** produced by the previously reported[42] intermolecular Stetter reaction catalyzed by *N*,*N*-dimethyl-

Scheme 8



Scheme 9





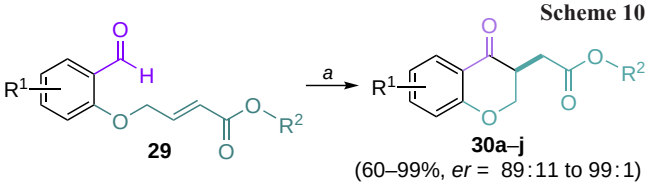
25a: Ar = Ph, EWG = CN (92%);
25b: Ar = 4-ClC$_6$H$_4$, EWG = CN (96%);
25c: Ar = 4-MeC$_6$H$_4$, EWG = CN (90%);
25d: Ar = Ph, EWG = COMe (90%);
25e: Ar = 4-ClC$_6$H$_4$, EWG = COMe (93%);
25f: Ar = 4-MeC$_6$H$_4$, EWG = COMe (88%);
25g: Ar = Ph, EWG = CO$_2$Et (88%);
25h: Ar = 4-ClC$_6$H$_4$, EWG = CO$_2$Et (92%);
25i: Ar = 4-MeC$_6$H$_4$, EWG = CO$_2$Et (85%);
25j: Ar = Ph, EWG = CO$_2$Me (89%);
25k: Ar = 4-ClC$_6$H$_4$, EWG = CO$_2$Me (90%);
25l: Ar = 4-MeC$_6$H$_4$, EWG = CO$_2$Me (86%)

benzimidazolium iodide catalyst **C′7** in a green solvent (water) or, alternatively, by the catalyst **C′7** under microwave irradiation. Reactions carried out in water without microwave assistance gave lower yields (58–77%) and were significantly more time-consuming, while those microwave-assisted carried out in a solvent-free fashion provided higher yields (85–96%). The hydration of hydroxide anions, which possibly prevents the production of carbenes, resulted in the reduced yields in water-assisted reactions. By breaking these hydrogen bonds, microwave irradiation increased the process efficiency by producing free hydroxyl ions and water molecules. Furthermore, the microwave assistance has been shown to be more efficient in producing 1,4-addition products as it could speed up the reaction up to 200 times compared with the thermally driven reaction. Catalyst **C′7** can be recycled up to four times in the solvent-free, microwave-assisted intermolecular Stetter reaction with just a little decrease in the product yield. This study contributes to the development of green chemistry by utilizing solvent-free methods and recyclable catalysts, minimizing waste and environmental impact. Furthermore, it expands synthetic possibilities, facilitates future research, and provides economic benefits through the cost-effective catalyst reuse.[45]

2.2. Enzyme-catalyzed Stetter reaction

In 2021, Chen *et al.*[46] reported the first stereoselective intramolecular Stetter reaction of (*E*)-4-(2-formylphenoxy)but-2-enoate **29** catalyzed by benzaldehyde lyase from *Pseudomonas fluorescens* (*pf*BAL) to afford 1,4-dicarbonyl products **30a–j** (Scheme 10). Screening of different enzymes using molecular dynamics (MD) simulations was performed to determine which thiamine diphosphate (ThDP)-dependent enzymes would be compatible with the model substrate, (*E*)-4-(2-formylphenoxy) but-2-enoate **29**, and *pf*BAL was found to be an effective enzyme due to its large active-site pocket compatible with the substrate. The intramolecular stereoselective Stetter reaction with a wide range of substrates **29** catalyzed by ThDP-dependent *pf*BAL enzyme in the presence of 20 mol.% methyl *tert*-butyl ether (MTBE) was investigated. It was found that substrates with electron-rich, electron-deficient, and electron-neutral substituents all successfully gave the desired products **30a–j** in high yields (60–99%) and with high stereoselectivity values (enantiomeric ratio (*er*) from 89:11 to 99:1). Its operational simplicity, mild reaction conditions, high yields and good stereoselectivity make it even more applicable than traditional chemical synthesis, offering a more sustainable and environmentally friendly way to produce important chiral products.

Scheme 10

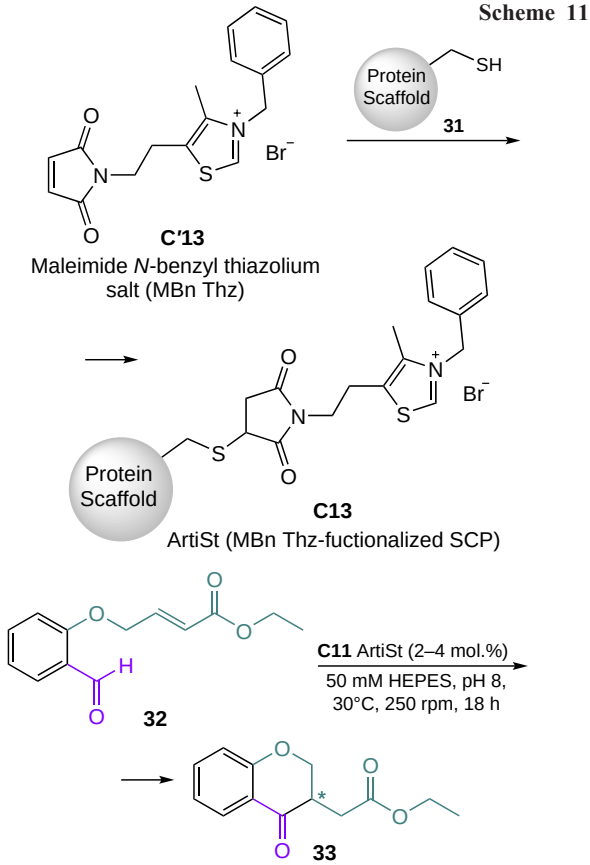


(*a*) *pf*BAL, ThDP, 20% MTBE

30a: R^1 = H, R^2 = Et (91%, *er* 98:2);
30b: R^1 = 8-Me, R^2 = Et (99%, *er* 99:1);
30c: R^1 = 6-Me, R^2 = Et (92%, *er* 99:1);
30d: R^1 = 6-OMe, R^2 = Et (99%, *er* 96:2);
30e: R^1 = 8-Cl, R^2 = Et (99%, *er* 98:2);
30f: R^1 = 8-Br, R^2 = Et (99%, *er* 89:11);
30g: R^1 = 6-Br, R^2 = Et (60%, *er* 95:5);
30h: R^1 = 6-F, R^2 = Et (99%, *er* 93:7);
30i: R^1 = H, R^2 = Me (99%, *er* 90:10);
30j: R^1 = 8-Me, R^2 = Me (99%, *er* 96:4)

In 2024, MacAulay *et al.*[47] functionalized a protein scaffold with a thiamine-inspired NHC to create an artificial enzyme, Stetterase (ArtiSt), which enabled a stereoselective intramolecular Stetter reaction under mild conditions with low catalyst loading. The steroid carrier protein (SCP) functionalized with maleimide *N*-benzyl thiazolium salt (MBnThz) **C13** was synthesized by modifying human steroid carrier protein (hSCP A100C) **31** with a thiazole-based NHC **C′13**, which was then tested as a catalyst. Substrate **32** was converted into Stetter product **33** using 2–4 mol.% ArtiSt (MBnThz-functionalized SCP) **C13**, 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) to maintain pH, at 30°C for 18 h under reflux conditions (Scheme 11). The study emphasized the importance of selecting the appropriate protein scaffold for optimizing catalytic activity. Targeted mutation (A100C) enabled successful functionalization, enhancing Stetter reaction

Scheme 11



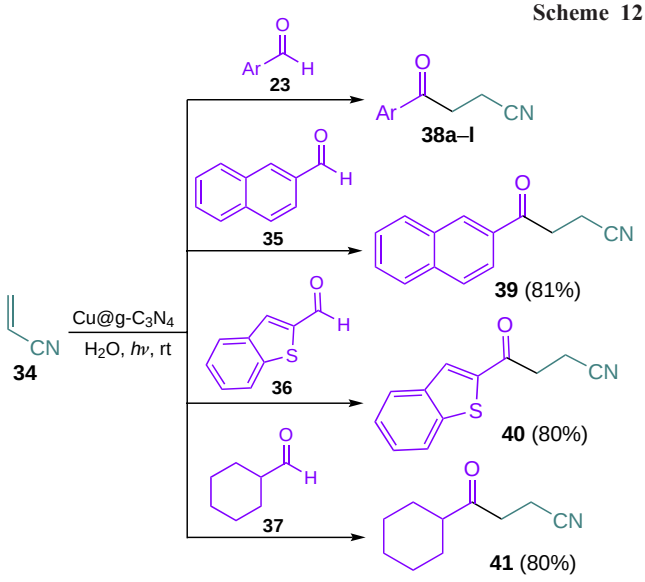
catalysis. *Thermus thermophilus* SCP (TTSCP) was identified as a promising scaffold and screening its different variants revealed that TTSCP L102C exhibited a 20-fold higher activity and highlighting its favorable structural and dynamic catalytic properties. In terms of stereoselectivity, the NHC-modified TTSCP L102C scaffold displayed low enantiomeric excess (*ee*) of 5% for the Stetter product, with a preference for the (*R*)-enantiomer as compared to the use of *pf*BAL, which provided 98% *ee* in the same reaction yielding predominantly the (*S*)-enantiomer. Nevertheless, ArtiSt is an interesting and quite promising catalyst; it still requires further improvement to achieve the high levels of efficiency and selectivity observed in natural catalytic systems.

2.3. Photocatalytic (visible light-mediated) Stetter reaction

In 2020, Rai *et al.*[48] reported the synthesis of γ-ketonitriles through a novel photocatalytic intermolecular Stetter reaction. The Stetter reaction between acrylonitrile **34** and variously substituted aromatic aldehydes **23**, **35**, **36** or aliphatic aldehyde **37** was catalyzed by Cu@g-C_3N_4 photocatalyst (PC) in water at room temperature under visible light irradiation to produce γ-ketonitriles **38a–l**, **39**–**41** in 80–95% yields (Scheme 12). No particular effect of the phenyl ring substituents was observed and even under the same conditions, aliphatic cyclic aldehyde **37** was converted into corresponding product **41** in 80% yield.

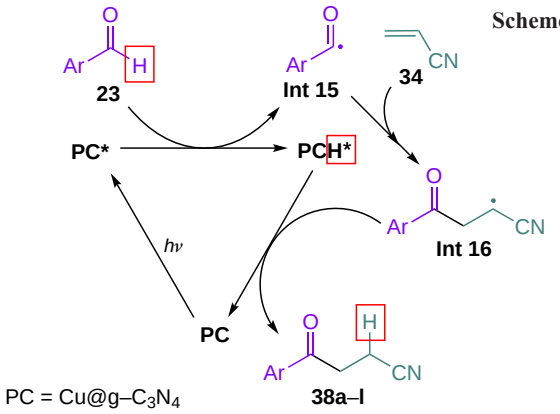
According to the proposed mechanism, the process starts when visible light converts PC (Cu@g-C_3N_4) into an excited state PC*, which abstracts hydrogen from aldehyde **23** *via* homolytic cleavage of the C–H bond to generate acyl radical **Int 15** and PCH* (Scheme 13). Acyl radical **Int 15** adds to α,β-unsaturated nitrile **34** to form the adduct radical **Int 16**, and the catalytic cycle is closed with the hydrogen transfer from PCH* to radical **Int 16** to afford the desired γ-ketonitrile product **38a–l**. The authors highlighted the versatility and the operational simplicity of the developed procedure, the wide substrate scope,

Scheme 12



38a: Ar = 4-ClC_6H_4 (94%); **38g**: Ar = 4-MeOC_6H_4 (86%);
38b: Ar = Ph (90%); **38h**: Ar = 4-Bu^tC_6H_4 (84%);
38c: Ar = 4-FC_6H_4 (89%); **38i**: Ar = 4-Cl$CH_2C_6H_4$ (87%);
38d: Ar = 4-BrC_6H_4 (95%); **38j**: Ar = 3-ClC_6H_4 (83%);
38e: Ar = 4-CNC_6H_4 (88%); **38k**: Ar = 3-MeC_6H_4 (82%);
38f: Ar = 4-MeC_6H_4 (87%); **38l**: Ar = 2-ClC_6H_4 (81%)

Scheme 13



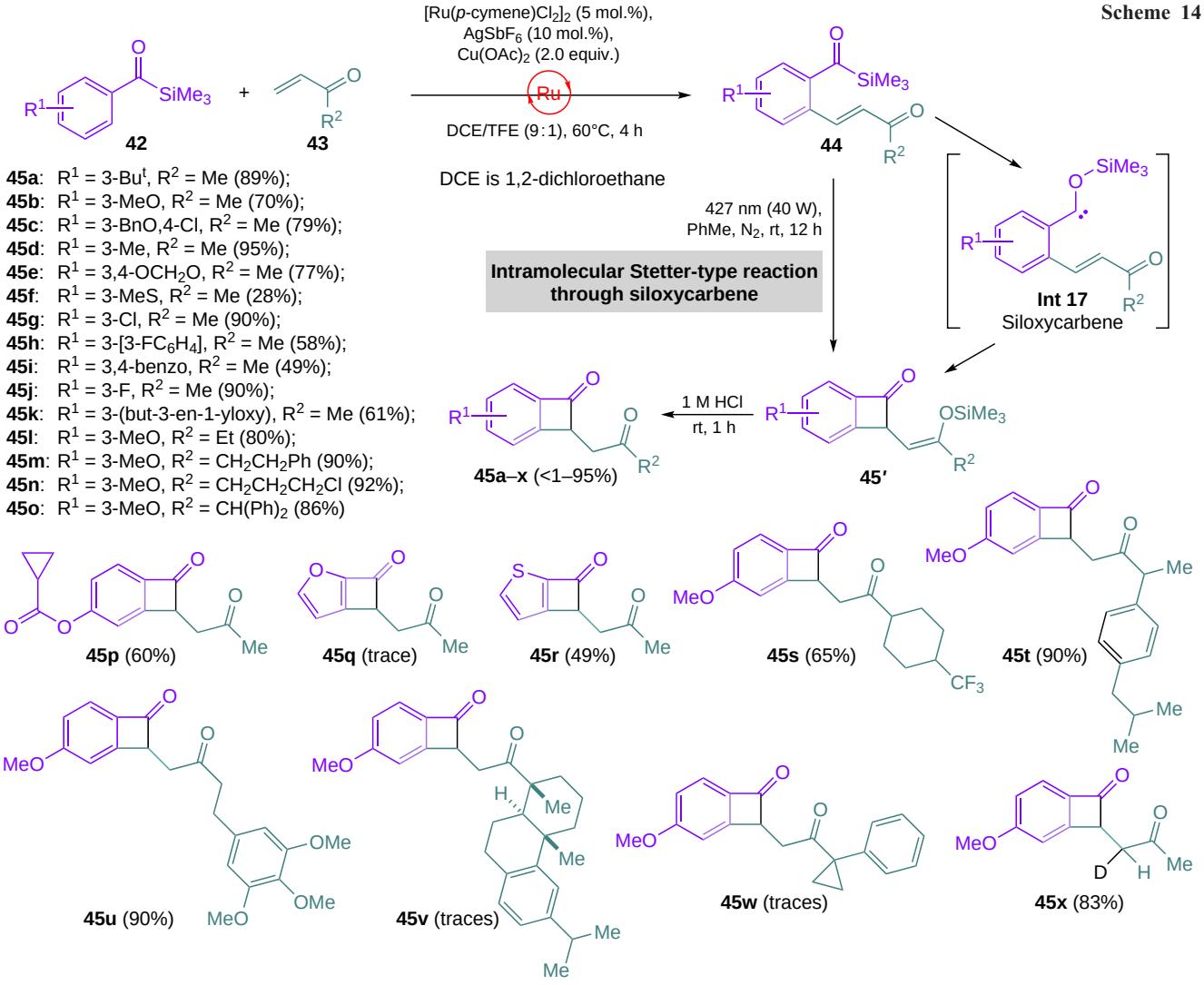
and the possibility of reusing the catalyst in multiple catalytic cycles. All this indicate its potential as a sustainable alternative for the synthesis of γ-ketonitriles.

Metal-catalyzed reactions are a very important tool in organic synthesis because they enable the efficient formation of complex bonds under mild conditions.[49] In 2024, Pilkington *et al.*[50] reported a novel synthetic strategy based on transition metal-catalyzed C–H functionalization of benzoylsilanes **42** followed by a photochemical Stetter-type reaction to construct benzocyclobutenone derivatives. First, olefinated acylsilanes **44** were produced by acylsilane-directed Ru(II)-catalyzed C–H olefination of benzoylsilanes **42** with vinyl ketones **43** in high yields and with high selectivity (Scheme 14). After that, acylsilane **44** undergoes visible-light-induced intramolecular Stetter-type reaction *via* the reactive siloxycarbene intermediate **Int 17** to give silyl enol ether **45′**. Subsequent hydrolysis of the latter affords benzocyclobutenone derivatives **45a–x**. This tandem reaction exploits the dual role of acylsilanes: as directing groups for C–H activation and as precursors for photochemically generated siloxycarbenes. A wide range of substrates was tested in this reaction, including various vinyl ketones and electron-rich and electron-deficient benzoylsilanes, and emphasized the function of trifluoroethanol (TFE) as a solvent to improve reaction yields. The proposed reaction mechanism involving the reversible 1,4-addition of the siloxycarbene to the tethered vinyl ketone and the irreversible silyl transfer was supported by DFT (Density functional theory) calculations. This method may find application in the synthesis of complex natural compounds and medicinal drugs. It should however, be noted that the photocyclization was relatively slow (12–24 h), and asymmetric applications remain unexplored. Nevertheless, this work represented a creative fusion of C–H activation and photochemical umpolung reaction, opening new avenues for carbene-mediated conjugate additions.

2.4. Stetter reaction using miscellaneous reaction conditions

The enantioselectivity in the intermolecular Stetter reaction has long been challenging for researchers, who utilized different NHC catalysts to achieve 1,4-dicarbonyl compounds in good yields. Bis(amino)cyclopropenylidenes carbenes (BACs) were proven to be very stable and effective catalysts for the intermolecular Stetter reaction,[51] and their outstanding performance gave rise to the synthesis of novel chiral backbones with high enantioselectivity. In 2021, Khalkhali *et al.*[52] synthesized unique chiral BAC catalysts **C′14–C′18** and described the first highly enantioselective intermolecular Stetter reaction between aldehydes and enones. Chiral pre-catalyst

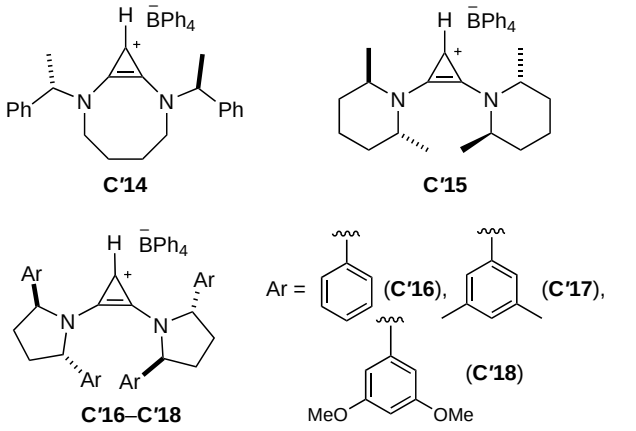
Scheme 14



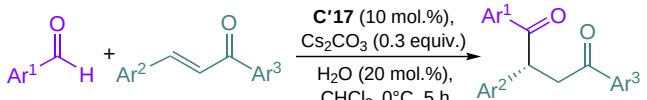
45a: R^1 = 3-Bu^t, R^2 = Me (89%);
45b: R^1 = 3-MeO, R^2 = Me (70%);
45c: R^1 = 3-BnO,4-Cl, R^2 = Me (79%);
45d: R^1 = 3-Me, R^2 = Me (95%);
45e: R^1 = 3,4-OCH$_2$O, R^2 = Me (77%);
45f: R^1 = 3-MeS, R^2 = Me (28%);
45g: R^1 = 3-Cl, R^2 = Me (90%);
45h: R^1 = 3-[3-FC$_6$H$_4$], R^2 = Me (58%);
45i: R^1 = 3,4-benzo, R^2 = Me (49%);
45j: R^1 = 3-F, R^2 = Me (90%);
45k: R^1 = 3-(but-3-en-1-yloxy), R^2 = Me (61%);
45l: R^1 = 3-MeO, R^2 = Et (80%);
45m: R^1 = 3-MeO, R^2 = CH$_2$CH$_2$Ph (90%);
45n: R^1 = 3-MeO, R^2 = CH$_2$CH$_2$CH$_2$Cl (92%);
45o: R^1 = 3-MeO, R^2 = CH(Ph)$_2$ (86%)

C′14 showed low enantioselectivity due to the C–N bond rotation. To restrict the rotation and improve enantioselectivity, C2-symmetric bulky amino substituents were used, which proved to be more effective than the use of fused rings. In comparison, piperidine-derived BAC catalyst **C′15** enhanced enantioselectivity at the expense of reactivity, while pyrrolidine-derived BAC catalysts **C′16**–**C′18** combined high selectivity with 92% conversion. Excellent yield of compound **48l** (95%) and high enantioselectivity of compound **48f** (92%) were achieved in the Stetter reaction between aromatic aldehyde **46** and enones **47** catalyzed by 10 mol.% chiral BAC catalyst **C′17** (Scheme 15). Interestingly, unexpectedly high enantioselectivities required a substoichiometric amount (20 mol.%) of water. The authors suggest that water molecules might form hydrogen bond networks stabilizing transition states, and also

Structures C′14–C′18



Scheme 15

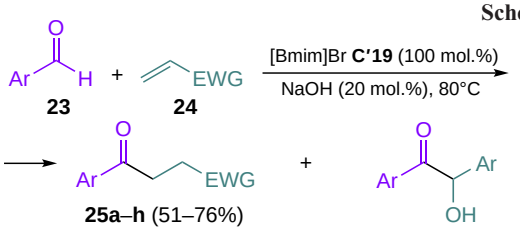


48a: Ar^1 = 4-CO$_2$MeC$_6$H$_4$, Ar^2 = Ph, Ar^3 = Ph;
48b: Ar^1 = 4-BrC$_6$H$_4$, Ar^2 = Ph, Ar^3 = Ph;
48c: Ar^1 = 4-CO$_2$MeC$_6$H$_4$, Ar^2 = 4-FC$_6$H$_4$, Ar^3 = Ph;
48d: Ar^1 = Ph, Ar^2 = Ph, Ar^3 = Ph;
48e: Ar^1 = 4-MeC$_6$H$_4$, Ar^2 = Ph, Ar^3 = Ph;
48f: Ar^1 = 4-CO$_2$MeC$_6$H$_4$, Ar^2 = 4-MeOC$_6$H$_4$, Ar^3 = Ph;
48g: Ar^1 = 3-MeOC$_6$H$_4$, Ar^2 = Ph, Ar^3 = Ph;
48h: Ar^1 = 2-Fu, Ar^2 = Ph, Ar^3 = Ph;
48i: Ar^1 = 4-CO$_2$MeC$_6$H$_4$, Ar^2 = 3-Fu, Ar^3 = Ph;
48j: Ar^1 = 4-CO$_2$MeC$_6$H$_4$, Ar^2 = Ph, Ar^3 = 2-Fu;
48k: Ar^1 = 3-Py, Ar^2 = Ph, Ar^3 = Ph;
48l: Ar^1 = 2-thiazolyl, Ar^2 = Ph, Ar^3 = Ph;
48m: Ar^1 = 2-benzofuryl, Ar^2 = Ph, Ar^3 = Ph;
Fu is furyl, Py is pyridyl

facilitate catalyst recovery in the Stetter reaction. The origin of enantioselectivity and the special role of water in the BAC-catalyzed Stetter reaction were investigated computationally. The BAC-catalyzed Stetter reaction tolerates a broad range of substrates, including differently substituted aldehydes and enones. Moreover, BACs have demonstrated the ability to catalyze 1,6-conjugate addition reactions, which expands the practical applicability, highlights their versatility and potential for wider applications of the above methodology in synthetic organic chemistry.

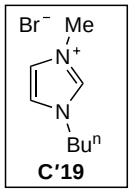
In 2020, Phungpis and Hahnvajanawong[43] reported the 1-butyl-3-methylimidazolium bromide ([Bmim]Br)-mediated Stetter reaction between aromatic aldehydes **23** and acrylonitrile or ethyl acrylate **24** in the presence of NaOH, where ([Bmim]Br) **C′19** acted both as a solvent and precatalyst generating the corresponding NHC *in situ* (Scheme 16). The reaction produced 1,4-addition products **25a–h** in good yields along with aroin derivatives **26a–d** as side products. Acrylonitrile was more reactive than ethyl acrylate in the Stetter reaction. Thus, [Bmim]Br proved to be a suitable catalyst for the Stetter reaction, enabling the production of key 1,4-dicarbonyl compounds, although with satisfactory selectivity.

Scheme 16



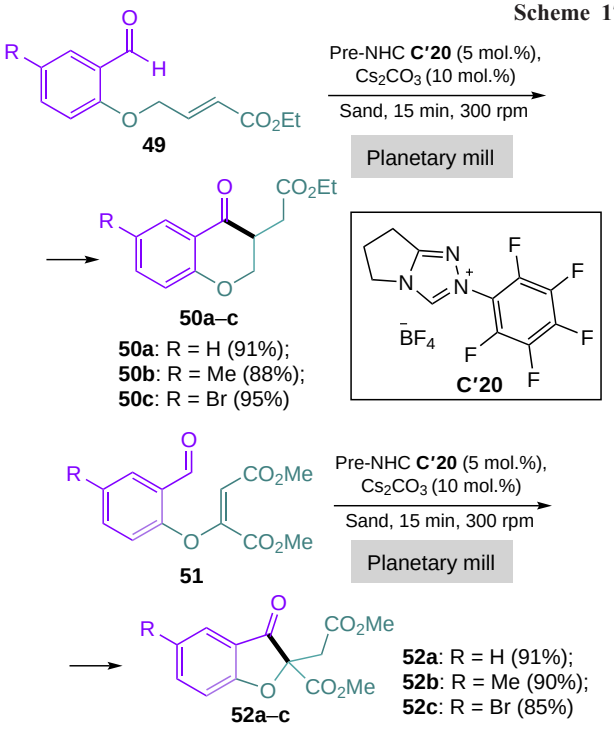
25a: Ar = Ph, EWG = CN (72%);
25b: Ar = 4-ClC$_6$H$_4$, EWG = CN (76%);
25c: Ar = 4-MeC$_6$H$_4$, EWG = CN (60%);
25d: Ar = C$_5$H$_4$N, EWG = CN (74%);
25e: Ar = Ph, EWG = CO$_2$Et (61%);
25f: Ar = 4-ClC$_6$H$_4$, EWG = CO$_2$Et (64%);
25g: Ar = 4-MeC$_6$H$_4$, EWG = CO$_2$Et (51%);
25h: Ar = C$_5$H$_4$N, EWG = CO$_2$Et (63%)

26a: Ar = Ph;
26b: Ar = 4-ClC$_6$H$_4$;
26c: Ar = 4-MeC$_6$H$_4$;
26d: Ar = 4-C$_5$H$_4$N;

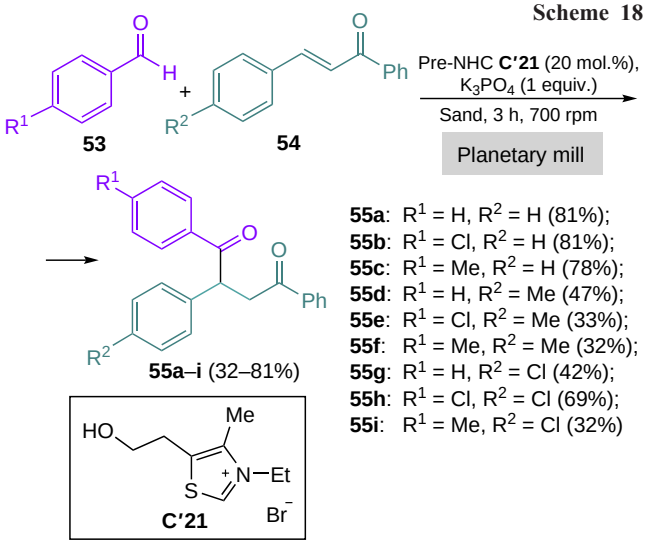


In 2020, Nicholson *et al.*[53] were the first to develop a mechanochemical modification of NHC-catalyzed intermolecular and intramolecular Stetter reactions. Various bases, grinding auxiliaries, precatalysts, and grinding speeds were screened to achieve optimal conditions for the acyl anion activation mode in intramolecular and intermolecular Stetter reactions. Intramolecular Stetter reaction catalyzed by 5 mol.% pre-NHC catalyst **C′20** under ball-milling conditions produced chromanone derivatives **50a–c** and 3-oxo-2,3-dihydrobenzofuran derivatives **52a–c** from compounds **49** and **51**, respectively, in good yields (Scheme 17). However, the pre-NHC catalyst **C′20** did not show satisfactory results in the intermolecular Stetter reaction. In this case, thiazolium catalyst **C′21** performed best in the intermolecular Stetter reaction between aromatic aldehydes **53** and chalcone **54** under ball-milling conditions to afford 1,4-diketones **55a–i** in moderate to good yields (Scheme 18). It was also found that an intramolecular Stetter reaction catalyzed by triazolium pre-NHC **C′22** under ball-milling conditions can proceed enantioselectively with up to 92% *ee* and in 96% yield (Scheme 19). NHC-catalyzed acyl anion mechanochemistry under ball-milling conditions offers a novel solvent-free

Scheme 17



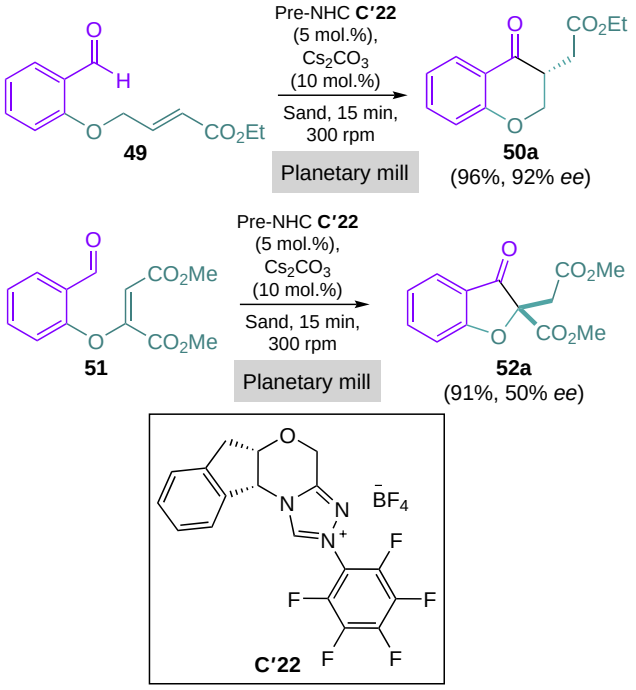
Scheme 18



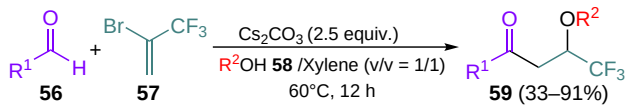
approach in organocatalysis. It enables diverse Stetter reactions with potential for high yields and enantioselectivity. However, challenges in optimizing yields, reproducibility, and reaction conditions highlight the need for further research to maximize the methodology's potential in practical applications.

In 2022, Cai *et al.*[54] reported a novel intermolecular Stetter reaction between aromatic aldehydes **56** and electron-deficient 2-bromo-3,3,3-trifluoropropene (BTP) **57**, catalyzed by the *in situ* generated α-trifluoromethyl carbanion **Int 19**. The reaction produces various β-alkoxyl-β-trifluoromethylated ketones **59** in moderate to high yields (Scheme 20). A variety of aliphatic/aromatic/heteroaromatic aldehydes and different alcohols were well tolerated and provided the desired products, except for an aliphatic aldehyde, which did not produce any product. The desired products were undetectable when ester, phosphate ester, sulfonyl, phenyl, and amide were used instead of α-trifluoromethyl group.

Scheme 19



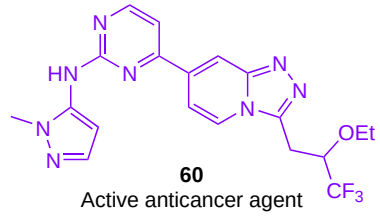
Scheme 20

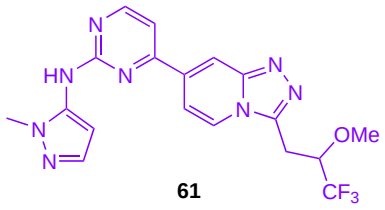


R^1 = 2-Naph, 1-Naph, Ph, 4-MeC_6H_4, 4-Bu^tC_6H_4, 4-MeOC_6H_4, 3,4-$(MeO)_2C_6H_4$, 3-MeOC_6H_4, 2-MeOPh, 4-CHCCH_2OC_6H_4, 4-CH_2CHCH_2OC_6H_4, 4-MeSC_6H_4, 4-Morpholinyl, 4-NHAcC_6H_4, 2-FC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-ethynyl-C_6H_4, 2-dibenzo[*b*,*e*]oxepin-11-one, 3-benzothiophene, 2-Fu, 2-Th, 2-quinoline;
R^2 = Me, Bn, 2-methylprop-1-enyl, 1-butynyl, cyclopropyl methyl, Pr^i;
Naph is naphthyl, Th is thienyl

The proposed mechanism includes first the formation of an alkoxy anion **Int 18** from alcohol **58**, then the alkoxy anion **Int 18** and BTP **57** react to form the α-trifluoromethyl carbanion catalyst **Int 19** (Scheme 21). The latter reacts with aldehyde **56** to produce an *O*-anion intermediate **Int 20**, which converts to the carbanion intermediate **Int 21** *via* a 1,2-proton transfer. Then, intermediate **Int 21** adds to BTP **57** to generate an unstable α-trifluoromethyl carbanion **Int 22**, which undergoes a 1,4-proton transfer to produce an *O*-anion intermediate **Int 23**. Intermediate **Int 23** releases α-trifluoromethyl bromide **Int 24** and regenerates the α-trifluoromethyl carbanion catalyst **Int 19**. Subsequent nucleophilic substitution of α-trifluoromethyl bromide **Int 24** by the alkoxy anion yields the final product **59**. This study introduced a novel umpolung strategy using an α-trifluoromethyl carbanion catalyst, enabling efficient C–C bond formation and high-yield synthesis of functionalized ketones, the further modification of which give rise to bioactive compounds, *e.g.*, potent anticancer agent I **60** and ERK (extracellular signal-regulated kinase) inhibitor II **61**. In addition, the trifluoromethyl group enhances the lipophilicity and stability of the resulting compounds, making them valuable for pharmaceutical and agrochemical applications. However, challenges such as intermediate stability, reaction specificity, complex mechanism, scalability, and limited substrates require further research and optimization.

Structures 60, 61

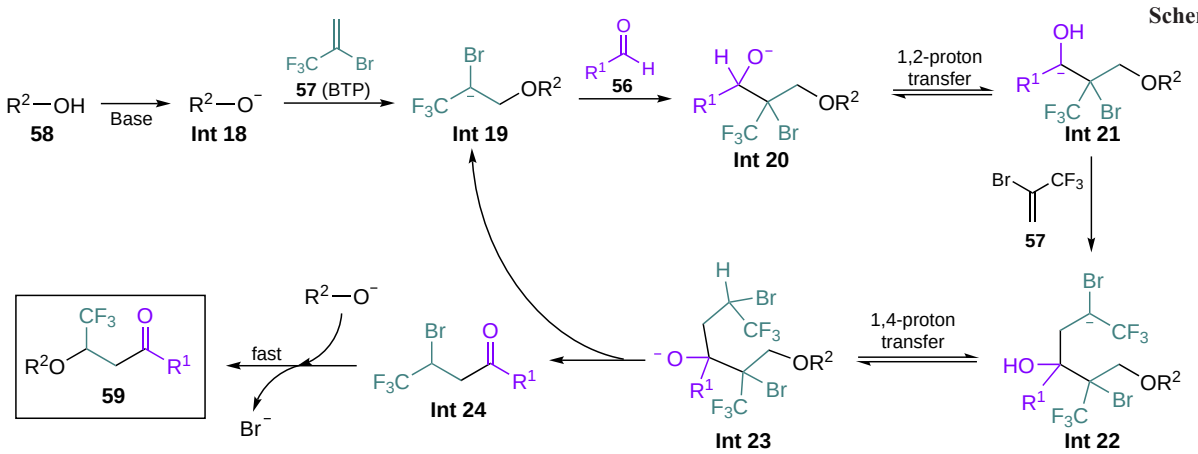




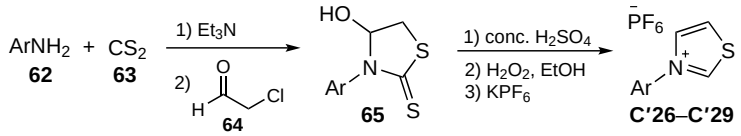
IC_{50} is half maximal inhibitory concentration

Since the discovery of the intermolecular Stetter reaction, it has been restricted only to the use of the aromatic aldehydes to produce 1,4-addition products along with acyloin by-products and till 2021, direct synthesis of aliphatic 1,4-diketones remained a synthetic challenge. In 2021, Brimble *et al.*[55] reported a new *N*-mesityl thiazolium NHC catalyst **C′29**, which demonstrated high performance in the intermolecular Stetter reaction of sterically non-trivial aliphatic aldehydes **1a–i** with enones **66**, **67** to generate 1,4-diketones **68a–i** and **69**, respectively (Scheme 22).[55] Both previously described **C′1**, **C′8**, **C′21**,

Scheme 21

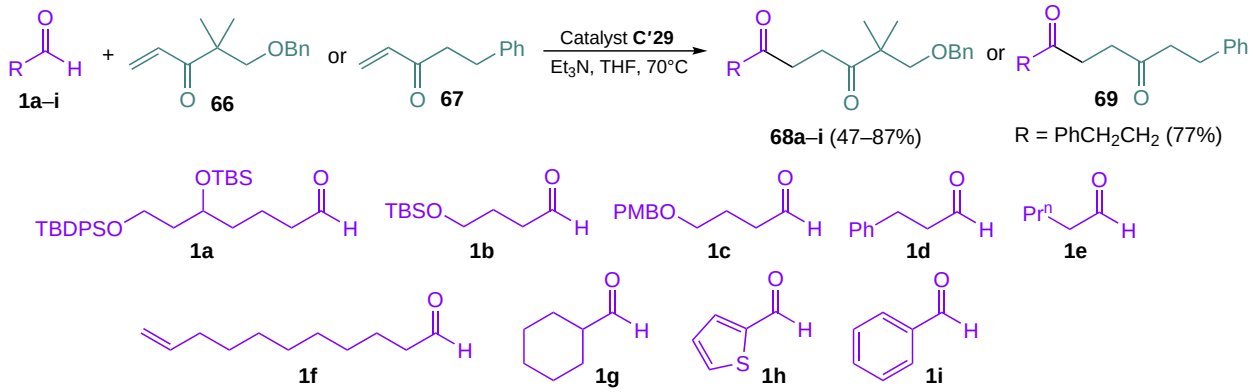


Scheme 22

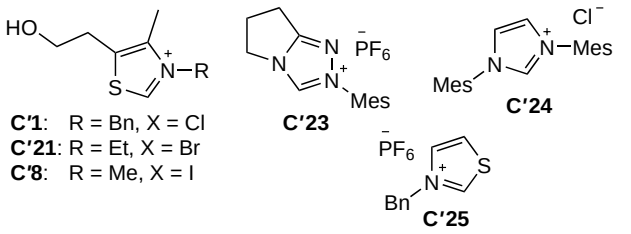


C′26: Ar = Ph (47%);
C′27: Ar = 4-MeOC$_6$H$_4$ (30%);
C′28: Ar = Dipp (23%);
C′29: Ar = Mes (59%)

Dipp is 2,6-diisopropylphenyl, Mes is mesityl, TBDPS is *tert*-butyldiphenylsilyl, TBS is *tert*-butyldimethylsilyl, PMB is *para*-methoxybenzyl



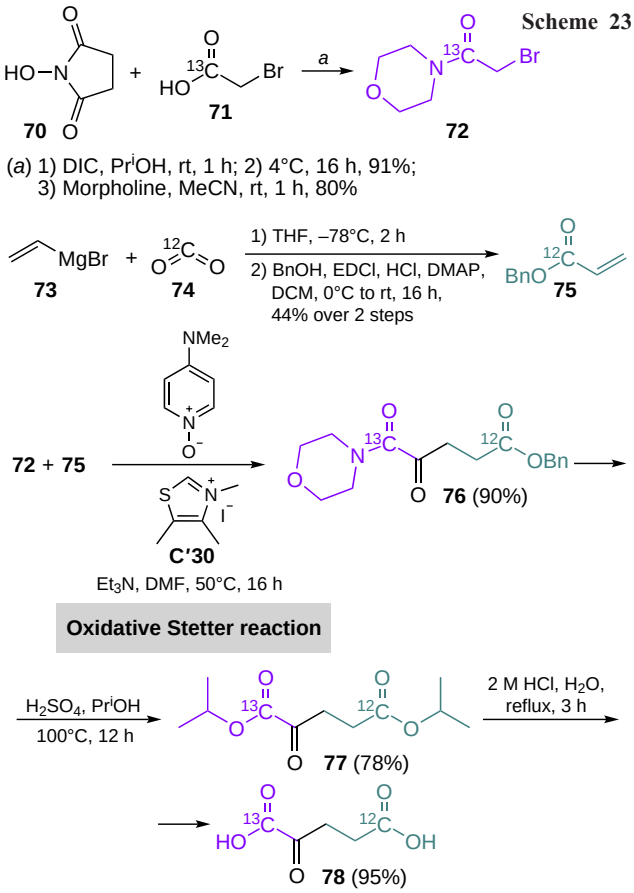
Structures C′1, C′8, C′21, C′23–C′25



C′23–**C′25** and novel catalysts **C′26**–**C′29** were tested in the intermolecular Stetter reaction of aliphatic aldehydes, and among these, the newly synthesized *N*-mesityl-substituted thiazolium catalyst **C′29** showed remarkable catalytic activity and good yield in just 30 minutes. For these substrates, catalyst **C′29** outperformed the conventional catalyst **C′1** in terms of both yields and reaction time, but its efficiency decreased in the case of aromatic aldehydes suggesting that its scope was only restricted to aliphatic systems. Percentage buried volume (%V_{Bur}) and σ-donating capacity were used as a quantification of the catalyst's steric and electronic properties, which affect its performance. The proposed method for percentage buried volume (%V_{Bur}) calculation provides useful parameter for the synthesis and screening of NHC catalysts thereby broadening their application in the synthesis of complex organic molecules under mild conditions.

α-Ketoglutarate (α-KG) is the substrate for the mutant isocitrate dehydrogenase 1 (IDH1) enzyme; unusual α-KG metabolism is associated with tumour cell differentiation and malignant development. IDH1 mutations cause the reduction of α-KG to 2-hydroxyglutarate (2-HG), which inhibits α-KG-dependent dioxygenases and have a number of other effects. Accurately detecting 2-HG in tumours using nuclear magnetic resonance (NMR), the challenge due to spectral overlap between naturally abundant [5-^{13}C]-α-KG and [1-^{13}C]-2-HG signals. The resulting [1-^{13}C-5-^{12}C]-α-KG eliminates signal overlap from naturally occurring [5-^{13}C]-α-KG. In 2021, Miura *et al.*[56] reported a new one-pot oxidative Stetter reaction between 2-bromo-1-morpholinoethan-1-one-1-^{13}C **72** and benzyl acrylate-1-^{12}C **75** catalyzed by thiazolium salt **C′30** and *N*-hydroxy-4-*N*,*N*-dimethylaminopyridine for *in situ* oxidation to form [1-^{13}C-5-^{12}C] α-ketoglutarate (α-KG) **78** (Scheme 23). The starting material **72** was synthesized from *N*-hydroxysuccinimide **70** and 1-^{13}C-labeled 2-bromoacetic acid **71**, activated with *N*,*N*′-diisopropylcarbodiimide (DIC) followed by substitution with morpholine. Benzyl acrylate-1-^{12}C **75** was obtained *via* the Grignard reaction of vinylmagnesium bromide **73** with ^{12}C–CO_2 **74**, followed by esterification to afford the product **75** in 44% yield over two steps. Under optimized

Scheme 23



DIC is *N*,*N*′-diisopropylcarbodiimide, EDCI is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP is 4-dimethylaminopyridine, DCM is dichloromethane

conditions, the one-pot oxidative Stetter reaction furnished compound **76** in 90% yield. Subsequently, the resulting compound **76** underwent a series of transformations to achieve the α-KG **78** in 95% yield. The novel [1-^{13}C–5-^{12}C]-α-ketoglutarate probe eliminates spectral overlap at C-5, enabling unambiguous detection of [1-^{13}C]-2-hydroxyglutarate in IDH1 mutant assays and HCT116 IDH1 R132H cells. This probe enhances diagnostic accuracy and offers a versatile tool for probing α-KG metabolism across diverse biomedical applications. However, its introduction into clinical practice requires additional research.

3. Natural products syntheses

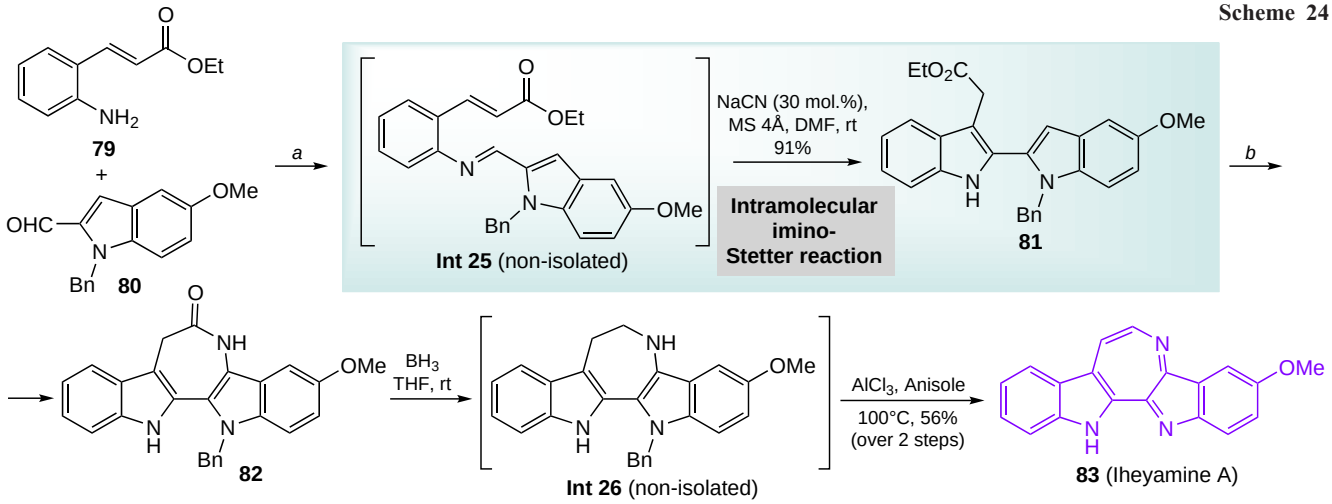
Synthesis of natural products involves constructing complex molecules found in nature using controlled chemical reactions.[57] Such studies facilitate a deeper understanding of molecular structures, functional behaviour, and their prospective applications in medicinal chemistry and biologically active compounds.[58–60]

3.1. Alkaloids

In 1999, Higa and co-workers[61] isolated iheyamines A and B containing azepino-2,2′-bisindole moieties from a colonial ascidian, *Polycitorilla sp*. from Iheya Island, Okinawa. Their limited bioavailability and cytotoxicity against cancer cells have sparked interest in their total synthesis. Till 2020, only three iheyamine A syntheses have been reported because producing the unsymmetrical 2,2′-bisindole scaffold with different substituents on each indole ring was the main difficulty in synthesizing iheyamines. Cross-coupling between two indole scaffolds or cyclization of uncyclized precursors to produce an unsymmetrical 2,2′-bisindole framework are two approaches that can address this issue. Iheyamine A was previously synthesized *via* cross-coupling between two indole scaffolds; however, this cyclization method did not allow the synthesis to be completed.[62–65] In 2020, Jeon *et al*.[66] described the second approach to the total synthesis of iheyamine A **83**, which involved first the reaction of ethyl 2-aminocinnamate **79** with *N*-benzyl-5-methoxyindole-2-carboxaldehyde **80** to give aldimine **Int 25**, which was not isolated (Scheme 24). Aldimine **Int 25** underwent the cyano-catalyzed imino-Stetter reaction to afford the unsymmetrical 2,2′-bisindole-3-acetate **81** in 91% yield. Next, compound **81** was converted into lactam **82** through nitrosylation (75% yield), reduction, and cyclization using NaOBu^t in 67% yield over two steps. In the next step, lactam **82** was reduced with BH_3 to afford *N*-benzyl tetrahydroiheyamine A **Int 26**, followed by debenzylation with $AlCl_3$ and subsequent aerobic oxidation to furnish finally iheyamine A **83** in 56% yield. This synthesis efficiently constructed the complex azepino-2,2′-bisindole core, with the imino-Stetter reaction being the key step.

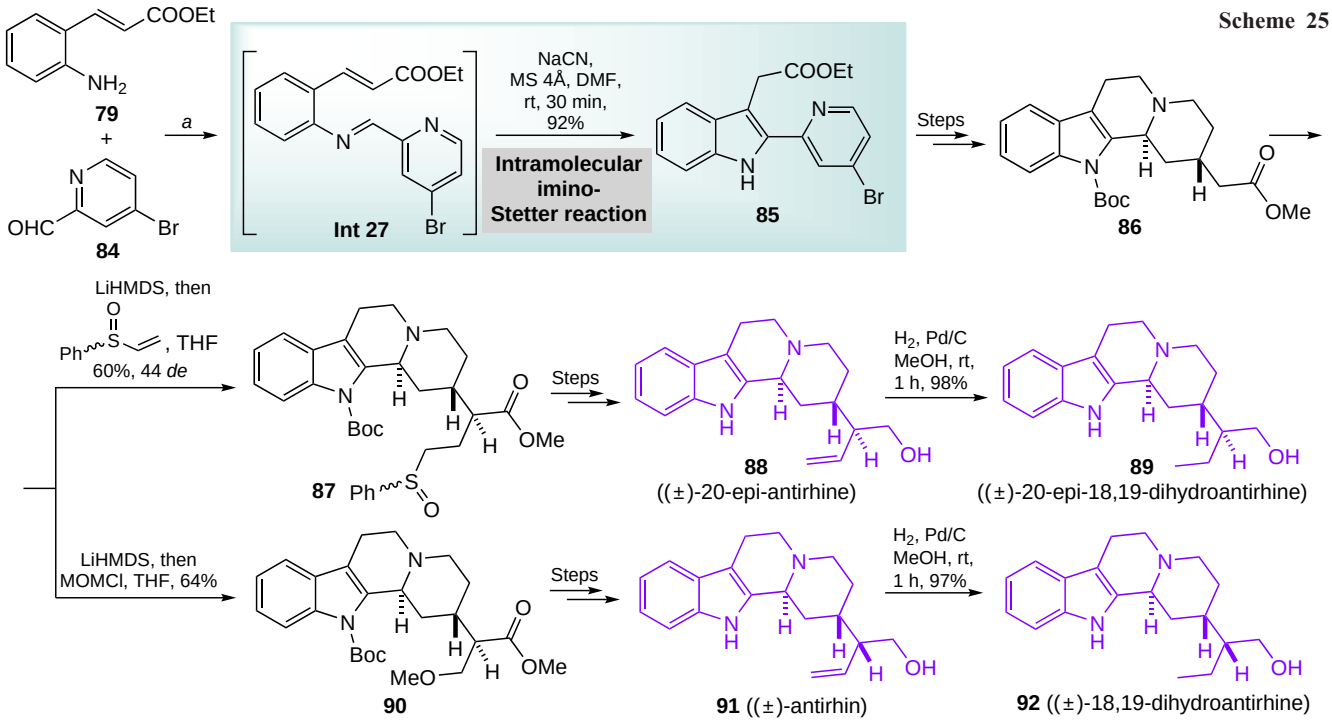
Antirhine, belonging to the Antirhine family of indole monoterpene alkaloids, possesses a tetracyclic indolo-quinolizidine structure with a distinctive C-18–C-19 vinyl/ethyl attachment on C-20 and a thermodynamically susceptible anti-relationship between C-3 and C-15 stereocentres.[67–69] Traditional synthesis of antirhine compounds was based on unique starting materials with predetermined stereochemistry at C-15 and C-20, resulting in specialized and non-generalizable methods. These procedures were often time-consuming and made it difficult to control stereochemical interactions, especially the *trans* configurations of C-3 and C-15.[70–75] A more efficient and adaptable synthesis using a common intermediate was required to overcome these issues. In 2020, Bae *et al*.[76] reported a novel total synthesis of (±)-20-epi-antirhine **88**, (±)-20-epi-18,19-dihydroantirhine **89**, (±)-antirhine **91**, and (±)-18,19-dihydroantirhine **92** through the cyanide-catalyzed imino-Stetter reaction (Scheme 25). The reaction between ethyl 2-aminocinnamate **79** and 4-bromopyridine-2-carboxaldehyde **84** gave compound **Int 27**, which was further subjected to the intramolecular imino-Stetter reaction catalyzed by NaCN in DMF in the presence of molecular sieves (MS) 4 Å to afford compound **85** in 92% yield. After a series of reactions, compound **85** was converted into the key indoloquinolizidine **86**, which was diverted into two different synthetic strategies. According to the first strategy, compound **86** was reacted with lithium hexamethyldisilazide (LiHMDS) followed by vinyl sulfoxide to give compound **87**, and after several steps, **87** was converted into 20-epi-antirhine **88**, which was further reduced to 20-epi-18,19-dihydroantirhine **89** in 98% yield. Compound **90** was obtained by the second strategy *via* the reaction of compound **86** with LiHMDS and then with methoxymethyl chloride (MOMCl). After a series of steps, **90** was transformed into antirhine **91**, which was further reduced to 18,19-dihydroantirhine **92** in 97% yield. The cyanide-catalyzed imino-Stetter reaction,

Scheme 24



(*a*) AcOH (10 mol.%), toluene, reflux; (*b*) 1) $NaNO_2$, AcOH, 75%; 2) PtO_2, H_2, MeOH; 3) NaOBu^t, MeOH, reflux, 67% (over 2 steps)

Scheme 25



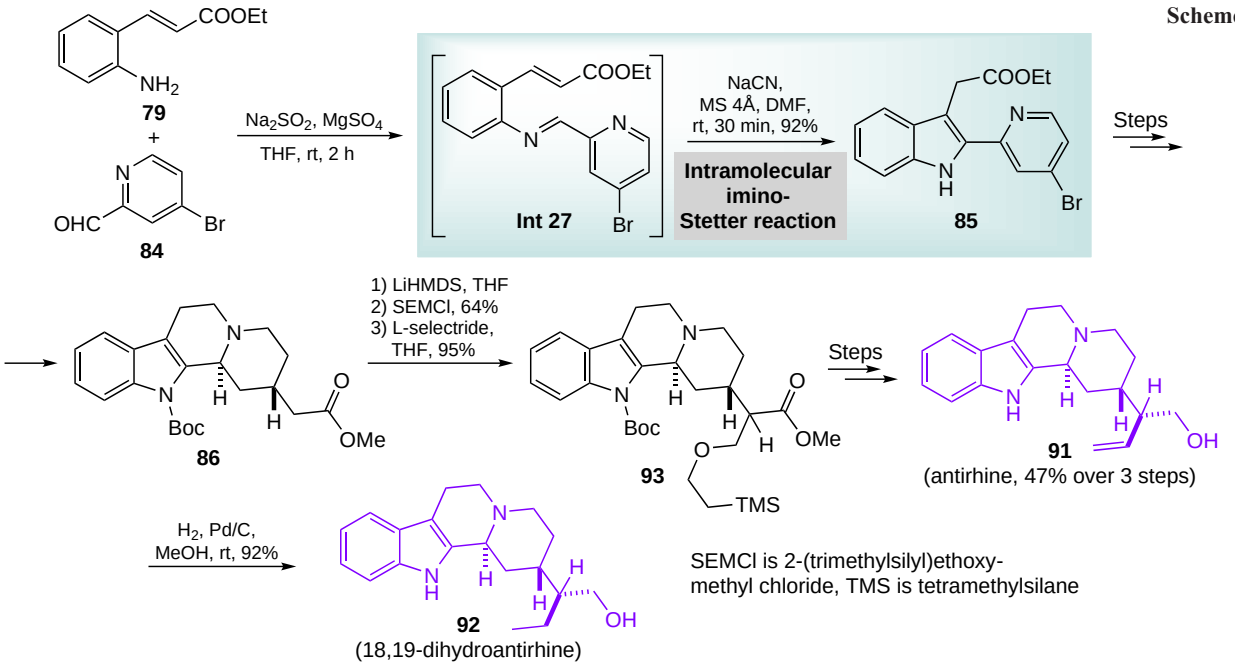
(*a*) Na_2SO_2, $MgSO_4$, THF, rt, 2 h; LiHMDS is lithium bis(trimethylsilyl)amide, MOMCl is methoxymethyl chloride

which produced derivatives of indole-3-acetic acid with a pyridine ring at position 2, was the key step providing 92% yield.

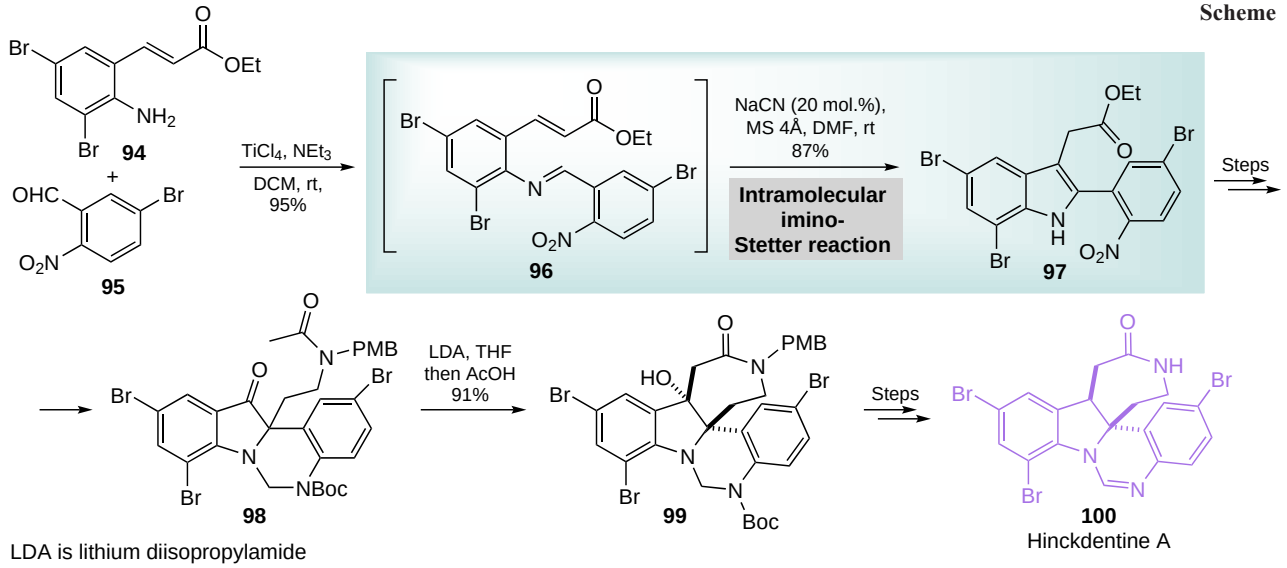
In 2021, Park *et al.*[77] reported a new synthetic approach to antirhine alkaloids through the cyanide-catalyzed Stetter reaction and the *trans*-selective installation of homoallylic alcohol side chain at the C-15 position. Various strategies for the synthesis of antirhine and its 20-epimers have been used, but satisfactory results have not been achieved. The synthesis began with the reaction of ethyl 2-aminocinnamate **79** with 4-bromopyridine-2-carboxaldehyde **84** to form the aldimine **Int 27** (Scheme 26). The intermediate **Int 27** underwent an intramolecular CN-catalyzed Stetter reaction to afford compound **85**. After that, compound **85** followed a series of reactions and formed a *trans*-indoloquinolizidine **86**, which was reacted with LiHMDS and 2-(trimethylsilyl)ethoxymethyl (SEM) chloride to give compound **93**. Intermediate **93** followed a series of reactions, *via* reduction of the ester with L-selectride, Dess-Martin oxidation, Wittig reaction, and deprotection to produce the desired product antirhine **91** in 47% yield over 3 steps. Antirhine **91** was reduced to 18,19-dihydroantirhine **92** in 97% yield. 20-Epi-antirhine **88** and 20-epi-18,19-dihydroantirhine **89** were synthesized according to the previously reported method.[76]

Hinckdentine A, containing a tri-brominated indolo[1,2-*c*]-quinazoline skeleton with a seven-membered lactam ring, was isolated from the marine bryozoan *Hincksinoflustra denticulata*

Scheme 26



Scheme 27

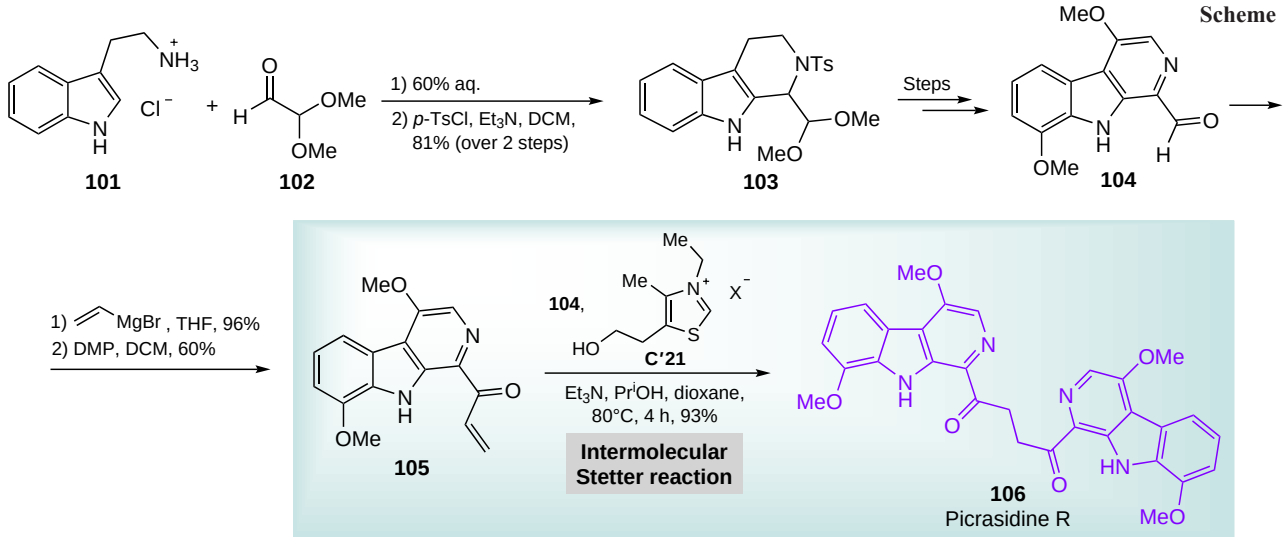


LDA is lithium diisopropylamide

in 1987.[78] Despite its extremely low isolated yield (0.0005%) and unexplored biological activity, its complex structure became a significant point of interest for synthetic chemists. Till 2021, there were three known total syntheses of Hinckdentine A, including two asymmetric approaches and one 8-desbromo-hinckdentine A total synthesis. In previous approaches, bromination was performed in the final step, but this led to inseparable mixtures of brominated compounds and required extra steps to control reactivity.[79–82] In 2021, Jeon *et al.*[83] reported a novel total synthesis using a starting material initially containing bromine atoms at the appropriate positions.[83] The reaction of ethyl 2-amino-3,5-dibromocinnamate **94** with 5-bromo-2-nitrobenzaldehyde **95** in the presence of $TiCl_4$, Et_3N, in DCM gave aldimine **96** (Scheme 27). This aldimine **96** was then subjected to the intramolecular CN-catalyzed imino-Stetter reaction, which led to 2-aryl-substituted indole-3-acetic acid ester **97** in 87% yield. Then, a series of steps *via* the formation of six membered-ring-containing compound **98** and seven-membered ring-containing compound **99** delivered Hinckdentine A **100**. The incorporation of bromine atoms during the synthesis of starting materials and the construction of the seven-membered ring *via* aldol condensation distinguishes this approach from previous methods. An asymmetric version of this total synthesis is currently under development.

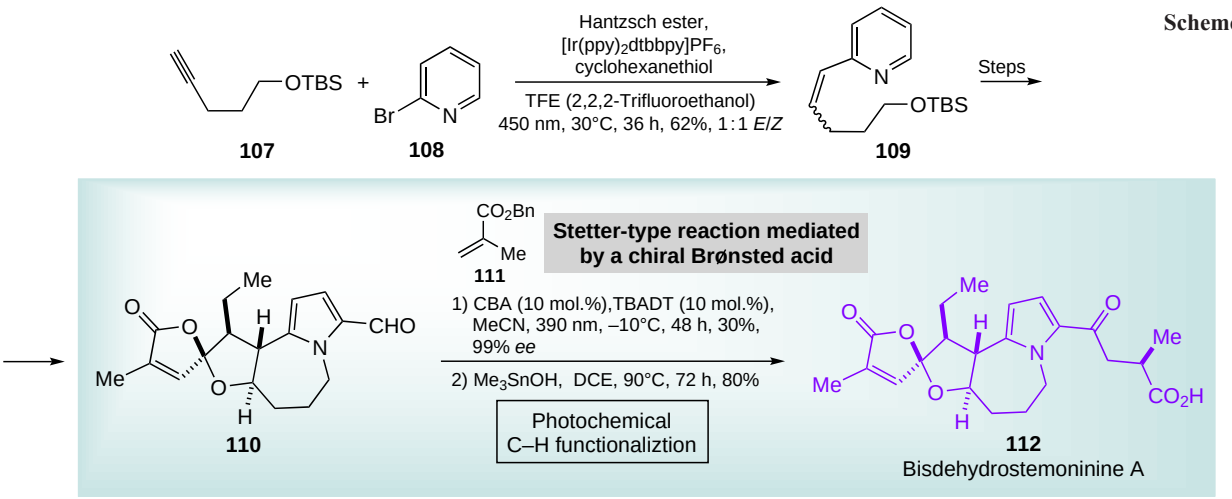
Numerous plants and animals contain β-carboline alkaloids, which have anti-inflammatory, anti-malarial, and anti-cancer effects. Many bis-β-carboline alkaloids from the *Simaroubaceae* family have already been identified.[84,85] Picrasidine R contains a 1,4-diketone linker between two β-carboline components, while picrasidines G, S, and T have an indolotetrahydro-quinolizinium (ITHQ) skeleton.[86–88] At room temperature, these alkaloids easily racemize in chloroform despite having a stereogenic core and often show cytotoxic activity.[89,90] In 2023, Wang *et al.*[91] reported the total synthesis of several bis-β-carboline alkaloids (Picrasidines I, G, R, S, and T), where picrasidine R was synthesized through a thiazolium-catalyzed Stetter reaction. The total synthesis commenced with the condensation of tryptamine hydrochloride **101** and 2,2-dimethoxy acetaldehyde **102** under acidic conditions to create the tetrahydro-β-carboline skeleton of the compound, which was then *N*-tosyl-protected to give compound **103** (Scheme 28). After that, compound **103** underwent a multi-step intramolecular reaction to form the fused bicyclic structure **104**. Vinylation of compound **104** through the Grignard reaction

Scheme 28



p-TsCl is *para*-toluenesulfonyl chloride, DMP is Dess-Martin periodinane

Scheme 29



followed by the Dess-Martin oxidation afforded compound **105**. Then, compounds **105** and **104** underwent a thiazolium **C′21**-catalyzed intermolecular Stetter reaction in the presence of Et_3N to give picrasidine R **106** in 93% yield.

Stemona alkaloids, traditionally recognized for their antitussive and insecticidal properties, exhibit notable structural and pharmacological diversity, primarily originating from Stemonaceae species.[92] While most members of this class contain saturated nitrogen-based heterocycles, a subset features oxidized pyrrole cores and a distinctive oxaspirocyclic butenolide motif. Previous total syntheses have elegantly accessed Stemona alkaloids *via* 12–22 step sequences. A central synthetic challenge across these efforts lies in the construction of the densely functionalized spirobutenolide-tetrahydrofuran ring system, which has consistently required nine or more steps to assemble.[93–96] In 2025, Akkawi and Nicewicz[97] reported innovative and efficient photochemically enabled total synthesis of three members of the Stemona alkaloid family (bisdehydrostemoninine, bisdehydrostemoninine A, bisdehydroneostemoninine), highlighting the power of photocatalysis to streamline complex natural product synthesis. The synthesis of bisdehydrostemoninine A **112** involved a Stetter-type reaction catalyzed by the hydrogen atom transfer (HAT) photocatalyst tetrabutylammonium decatungstate (TBADT), facilitated with a chiral Brønsted acid (CBA). The synthesis was initiated by the photoredox hydroarylation reaction between alkyne **107** and 2-bromo-pyridine **108**, yielding a mixture of (1 : 1 *E*/*Z*) alkene isomers **109** (Scheme 29). This mixture then underwent a series of steps to form the compound **110**. The synthesis of bisdehydrostemoninine A **112** was initially considered as a Stetter reaction, but formyl pyrroles proved incompatible with typical NHC catalysts. To overcome this, TBADT-mediated photochemical C–H functionalization with Giese acceptors was followed, which required a diastereocontrolled chiral catalyst. So, the photochemically-assisted Stetter-type reaction of compounds **110** and **111** catalyzed by 10 mol.% TBADT using 10 mol.% CBA resulted in the sterocontrolled formation of bisdehydrostemoninine A **112**.

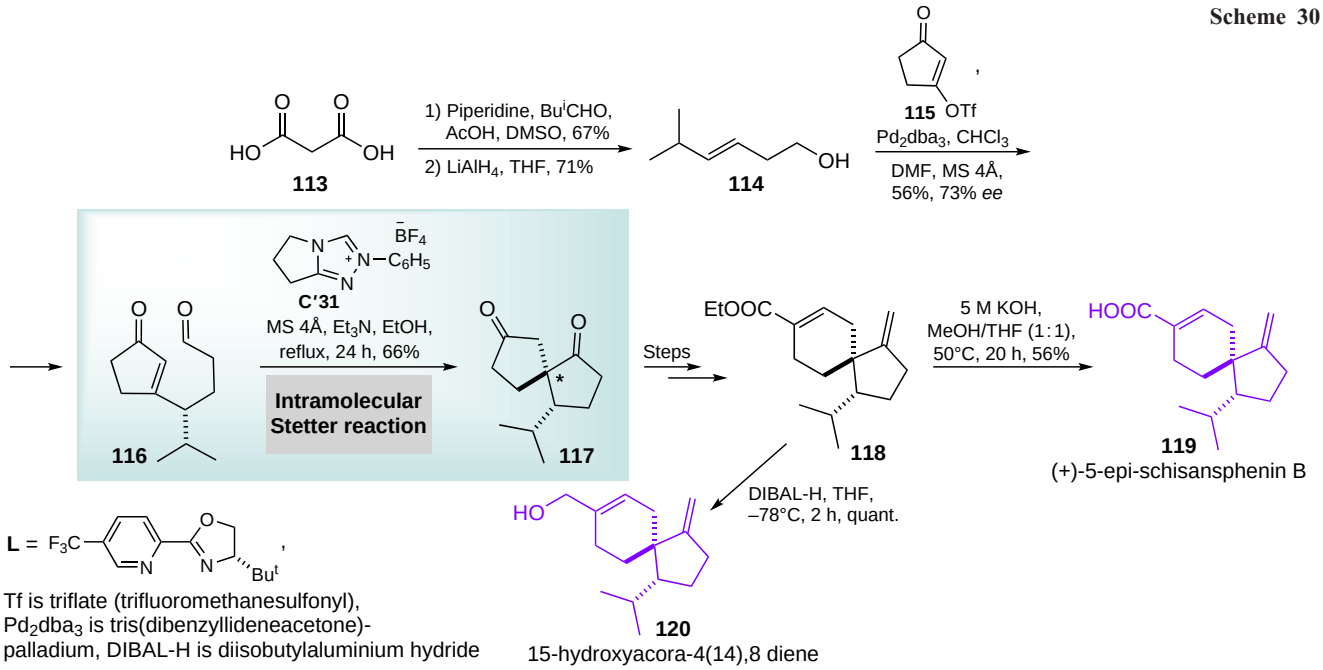
3.2. Sesquiterpenes

Methods for the isolation and purification of the spiro[4.5]-decanecarbon core-containing acorane-alaskan sesquiterpenes, schisansphenin B from *Schisandra sphenanthera* (2011) and 15-hydroxyacora-4(14),8-diene from *Juniperus chinensis* (1996) were reported. Schisansphenin B demonstrates significant immune modulatory activity, but no biological effects have been reported for 15-hydroxyacora-4(14),8-diene. Despite sharing an identical carbon skeleton, the two compounds differ in the stereochemical orientation of the double bond within the six-membered ring and the positioning of the isopropyl group; however, their absolute configurations have yet to be definitively established.[98–100] The primary challenge in synthesizing acorane-type natural products lies in the precise asymmetric installation of the anticipated stereostructures on the spiro quaternary carbon atom and the adjacent chiral centres. A comprehensive literature review indicates that various synthetic strategies have been explored to construct the acorane skeleton effectively.[101–105] In 2022, Hsu *et al.*[106] reported a new synthetic approach for the total synthesis of (+)-5-epi-schisansphenin B **119** and proposed the structure of (+)-15-hydroxyacora-4(14),8-diene **120** (Scheme 30). The synthesis started from malonic acid **113**, which was converted into (*E*)-5-methylhex-3-en-1-ol **114** over two steps. After that, compound **114** was reacted with triflate **115** to give enantioselective enone-aldehyde **116** through the palladium-catalyzed redox-relay Heck alkenylation. Then, enone-aldehyde **116** underwent an intramolecular Stetter reaction catalyzed by the triazolium salt **C′31** to yield spirocyclic 1,4-dione **117**. After a series of reactions, compound **117** was converted into compound **118**, which was hydrolyzed to (+)-5-epi-schisansphenin B **119**. On the other hand, (+)-15-hydroxyacora-4(14),8-diene) **120** was produced by using DIBAL-H to reduce the compound **118** ester group to alcohol. The formation of spirocyclic 1,4-dione was the crucial step in the synthesis. This was achieved by three types of reactions, but the intramolecular Stetter reaction proved to be the most successful.

3.3. Miscellaneous

Perylenequinone-derived natural products are divided into two main classes: fully conjugated perylenequinones like calphostins and hypocrellins, and those partially reduced (di-, tetra-, or hexahydroperylenequinones) such as altertoxins.[107–113] The latter are fungal metabolites with toxic relevance, often lacking additional carbon substituents and featuring methylated hydroxy groups and till 2024, no total synthesis has been achieved for these compounds despite efforts. Altertoxins are important metabolites of fungi that are divided into two subtypes, the biphenyl-type (altertoxin I, II, stempyltoxin I) and the dihydroanthracene-type (*e.g.*, altertoxin III), which feature two stacked benzene rings and two diagonally oriented benzene

Scheme 30

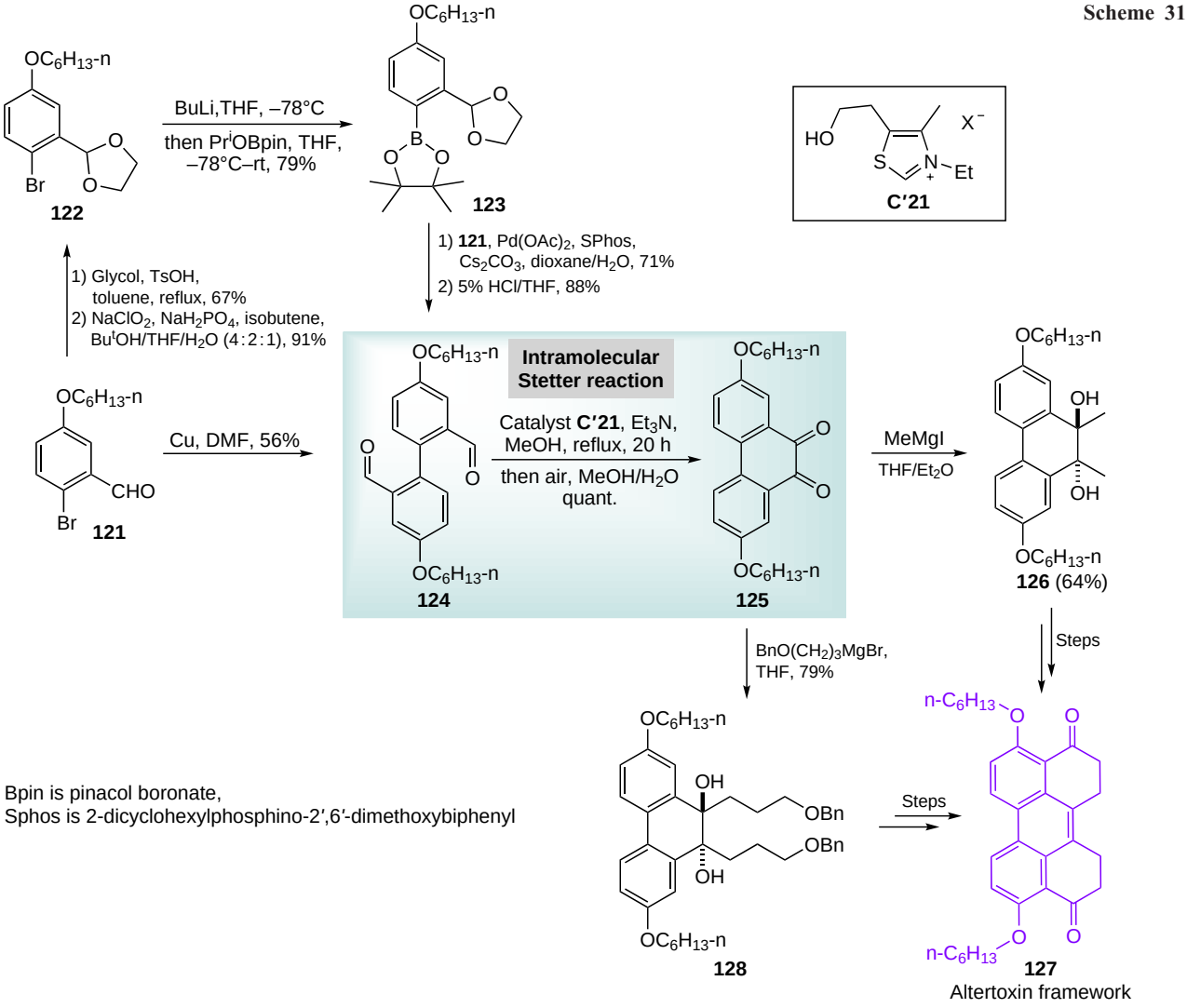


rings, respectively.[113,114] In 2024, Gutsche *et al.*[115] described the syntheses of altertoxin I framework by following different synthetic routes; one route involved the formation of the phenanthrenequinone through the intramolecular Stetter reaction. In the first step, the starting material, bromobenzaldehyde **121**, was converted into the biphenyl dialdehyde compound **124** by the direct Ulmann reaction (Scheme 31). In an alternate approach, bromobenzaldehyde **121** was protected by an acetal formation (compound **122**), which was boronated to give the intermediate **123**, followed by the Suzuki coupling and transformation to biphenyl dialdehyde **124**. The latter compound **124** underwent an intramolecular Stetter reaction catalyzed by thiazolium salt **C′21** in the presence of triethyl amine and methanol to form cyclized acyloin, which was immediately converted into phenanthrenequinone **125** through oxidation. Compound **125** was reacted with MeMgI to form the *trans* diastereoisomer of pinacol **126** which was converted into Altertoxin I framework **127** after a series of steps. In another approach, compound **125** was reacted with 3-benzyloxypropyl magnesium bromide to form compound **128** which was also expected to afford Altertoxin I **127**, but the authors did not completed this synthetic route.

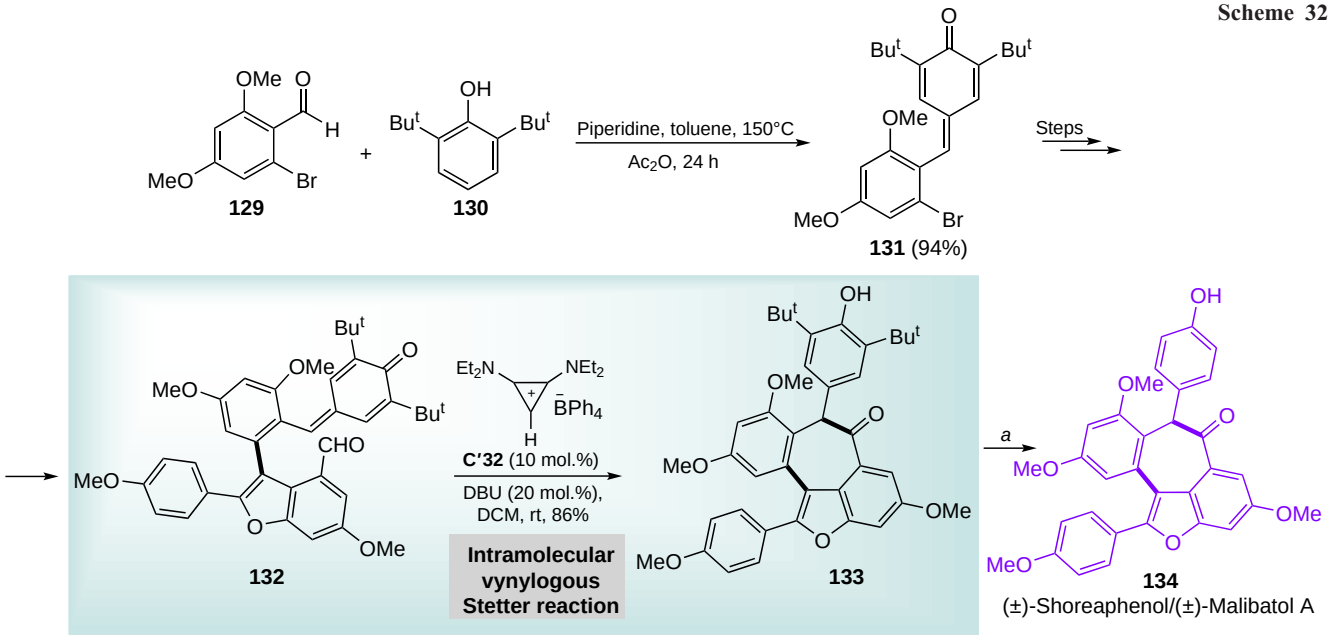
In 1998, Boyd and co-workers[116] isolated two novel oligostilbenes, malibatols A and B, from *Hopea malibato* leaves, which showed significant cytotoxic activity against CEM-SS cells in antiviral assays. Shoreaphenol (or hopeafuran), an oxidized structural derivative of malibatol A, was subsequently isolated from Shorea robusta and Hopea utilis.[117,118] Despite their promising bioactivity and unique carbon frameworks, attempts to synthesize these oligostilbene natural products remain sporadic.[119–122] In 2024, Ranga *et al.*[123] reported a new approach to 9-phenanthrol derivatives from 2-(2-formylaryl)-aryl substituted *p*-quinonemethides (*p*-QMs) catalyzed by bis(aminoalkyl)cyclopropenylidene (BAC) through the intramolecular vinylogous Stetter reaction. In addition, this approach was effectively used to create the seven-membered (±)-shoreaphenol and (±)-malibatol A **134**, natural products based on resveratrol. The synthesis of (±)-shoreaphenol and (±)-malibatol A **134** commenced with the reaction of 2-bromo-4,6-dimethoxybenzaldehyde **129** and 2,6-di-*tert*-butylphenol **130** to give 2-bromoaryl-substituted p-QM **131**, which was converted into intermediate **132** *via* a series of reactions (Scheme 32). The resulting intermediate **132** was then subjected to an intramolecular annulation (vinylogous Stetter reaction) catalyzed by 10 mol.% BAC **C′32** and 20 mol.% DBU to produce seven-membered carbocycle **133**. After that, intermediate **133** was subjected to $AlCl_3$ in benzene to remove the protecting *t*-butyl group and form key structure **134**. This methylated shoreaphenol derivative **134** may be used to synthesize (±)-shoreaphenol and (±)-malibatol A natural product.

Furancarboxylic acids, in particular penicilfuranone A, represent a class of bioactive aromatic polyketides with complex tricyclic frameworks and multiple stereocentres, including challenging quaternary centres. Isolated from *Penicillium* sp. sh18, penicilfuranone A exhibits potent antifibrotic activity and poses significant synthetic challenges due to its highly oxidized benzocyclohexanone core and acid-sensitive tertiary alcohol moiety.[124] Its biosynthesis was proposed to proceed *via* gregatin A and phenol intermediates, involving a sequence of Michael and aldol additions followed by benzylic oxidation. A key transformation includes a vinylogous internal substitution (S_Ni) reaction that forms a quaternary stereocentre through an enantioselective internal substitution.[125] In 2025, Ding *et al.*[126] reported the NHC-catalyzed asymmetric synthesis of penicilfuranone A **143** through a Stetter-aldol cascade reaction. The synthesis commenced with the preparation of an aromatic aldehyde **137** derived from diphenol **135** (Scheme 33). The OH group of compounds **135** was first protected with an allyl group using allyl bromide and potassium carbonate, and then the aldehyde group was reduced to a primary alcohol moiety with sodium borohydride to give compound **136**. Next, treatment with BuLi generated an aryllithium species, which reacted with acetaldehyde to install a secondary alcohol at the benzylic position, producing compound **137** in 72% yield. At the same time, an aliphatic unsaturated ketone **138** underwent an asymmetric cyanosilylation catalyzed by (*S*,*S*)-Al-salen, yielding a chiral cyanohydrin **139**, which was further converted to gregatin A **140**. Compounds **137** and **140** were then subjected to a key NHC-catalyzed Stetter–aldol cascade reaction in the

Scheme 31

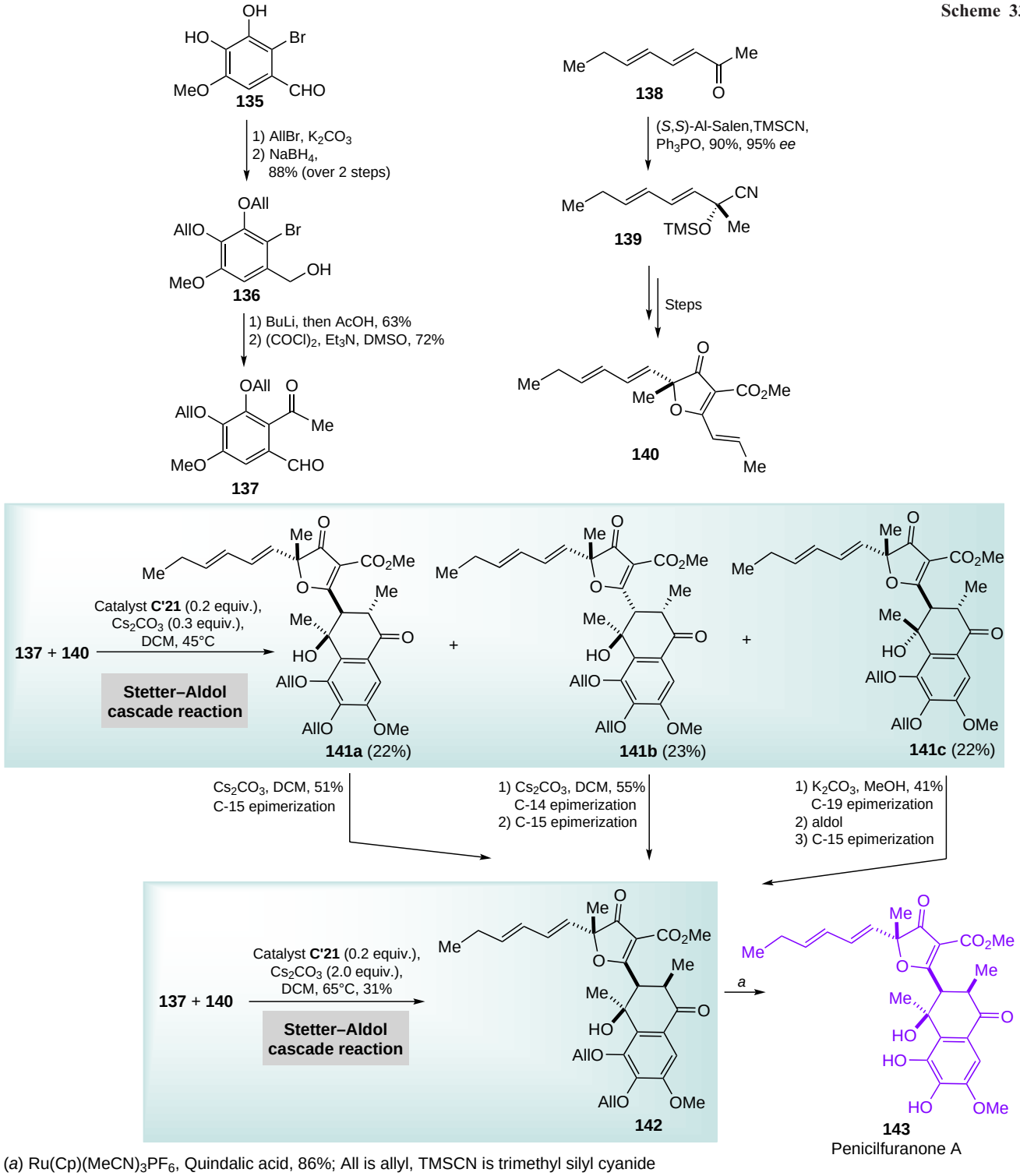


Scheme 32



(*a*) $AlCl_3$, PhH, 40°C, 6 h, 79%

Scheme 33



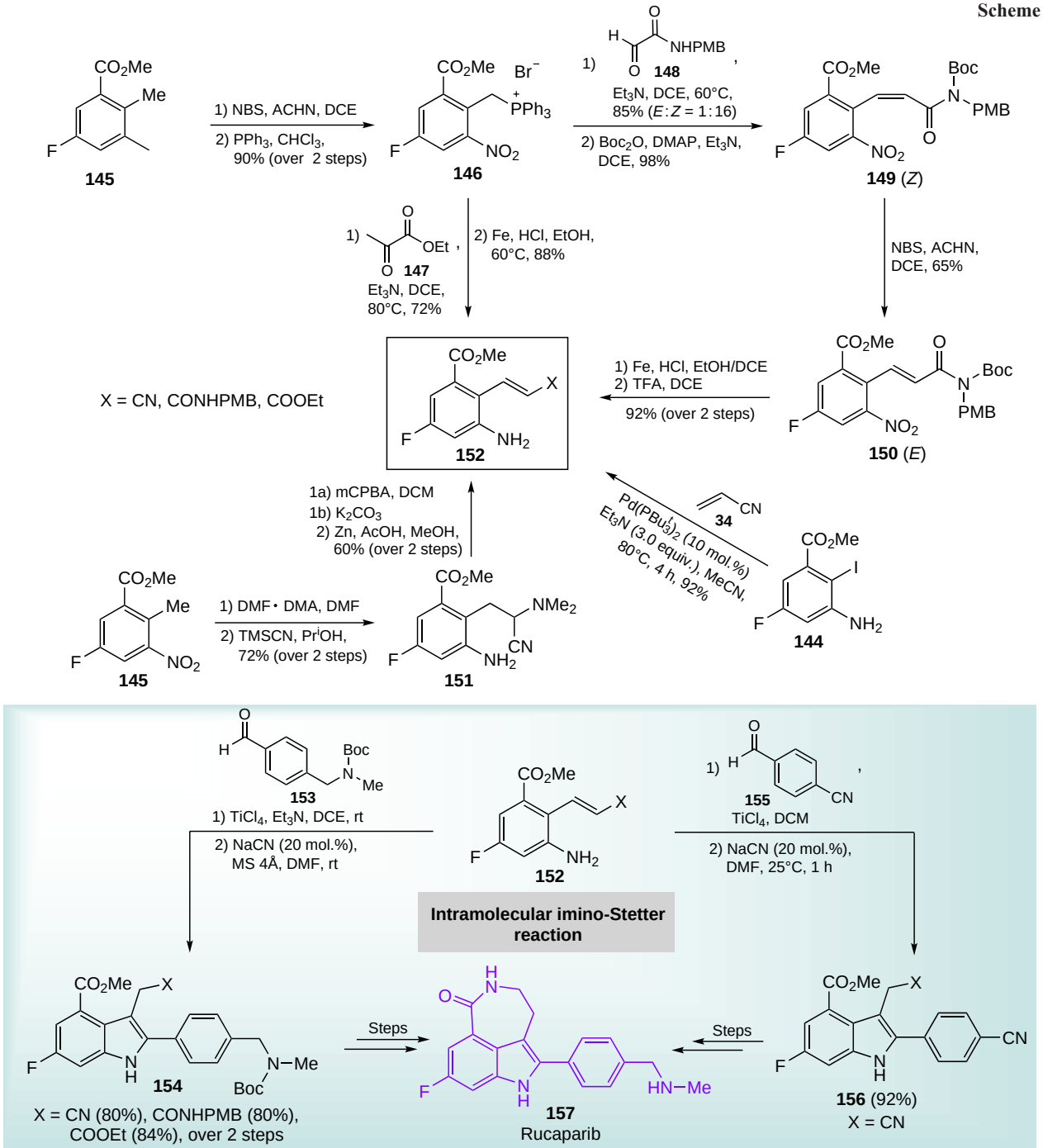
(*a*) Ru(Cp)(MeCN)$_3$PF$_6$, Quindalic acid, 86%; All is allyl, TMSCN is trimethyl silyl cyanide

presence of cesium carbonate and DCM. Herein, the NHC-catalyzed umpolung strategy was followed, where a carbene catalyst activated benzaldehyde to generate a nucleophilic Breslow intermediate. This intermediate underwent a formal [4+2] annulation with an electron-deficient alkene (gregatin A), facilitating the formation of the skeleton with high stereoselectivity *via* a Stetter–Aldol cascade reaction. This step rapidly constructed the highly oxygenated and stereochemically dense benzocyclohexanone ring system that mimics the B-ring of penicilfuranone A. Due to the complexity of the system, several diastereomers **141a**, **141b**, **141c** and **142** were formed, prompting selective epimerization at C-15, and in some cases, sequential epimerization at C-14, C-15, and C-19 to achieve the desired stereochemical configuration **142**. The final step involved selective deallylation and subsequent transformations to install the stereocentres, culminating in the asymmetric total synthesis of penicilfuranone A **143**, with the Stetter reaction playing a crucial role in forming the core framework through the umpolung approach. In addition to simplifying the synthesis of penicilfuranone A **143**, this novel synthetic method provides possibilities for the production of other 4-hydroxytetralone-containing natural products.

4. Syntheses of drugs

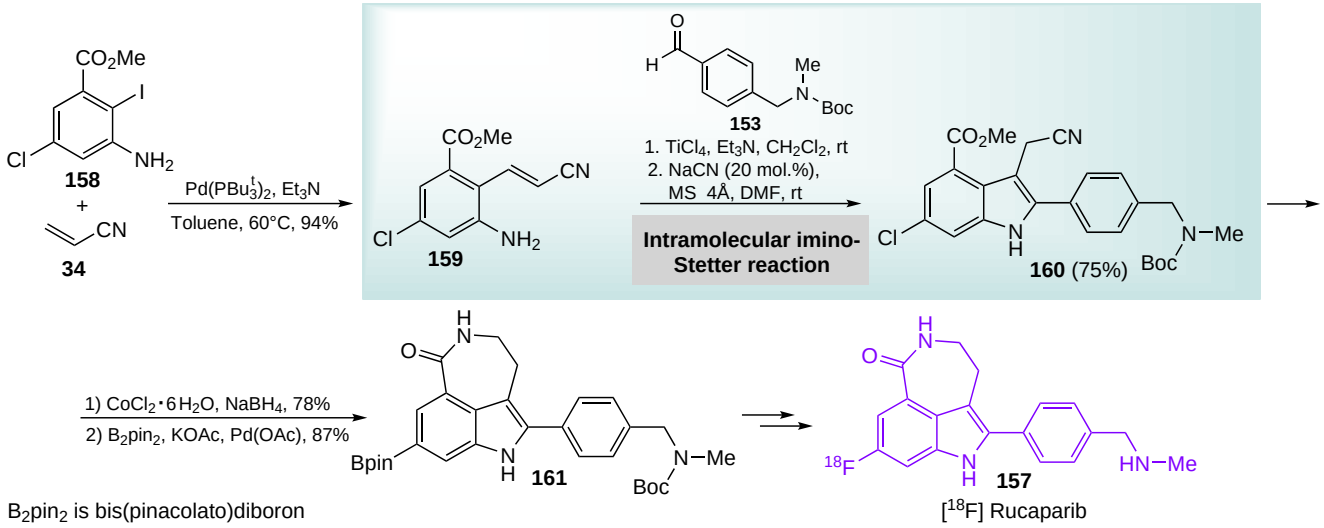
Poly(ADP-ribose) polymerase inhibitor (PARP) rucaparib is approved for ovarian and prostate cancer treatment and is undergoing clinical trials for other cancers.[127–129] Its structure features a highly substituted indole core fused with a seven-membered lactam ring. Due to the challenge of obtaining indole derivatives with precise substitutions, previous syntheses were based on constructing the indole core from *meta*-fluorobenzoic acid derivatives.[130–132] In 2022, Park and Cheon[133] reported a concise total synthesis of rucaparib by the Heck reaction of commercially available reactants, aryl iodide **144** and acrylonitrile **34**, which gave (*E*)-2-aminocinnamonitrile **152** (Scheme 34). Next, compound **152** was reacted with aldehyde **153** to give an aldimine, which further underwent the intramolecular CN-catalyzed imino-Stetter reaction to afford indole-3-acetonitrile **154** in 80% yield. After a series of steps, rucaparib **157** was obtained. This synthetic route has the advantage of using commercially available starting materials and achieving the total synthesis of rucaparib in only three separation steps with an overall yield of 54%. The same year, the authors[134] reported another two approaches for the concise synthesis of rucaparib from commercially available starting materials based on the cyanide-catalyzed imino-Stetter reaction as a key step. The synthesis commenced with the reaction of the commercially available starting material, *meta*-fluorobenzoate **145**, with *N*-bromosuccinimide (NBS), followed by the addition of triphenylphosphine to produce the intermediate phosphonium

Scheme 34



NBS is *N*-bromosuccinimide, ACHN = 1,1′-azobis(cyclohexanecarbonitrile), TFA is trifluoroacetic acid

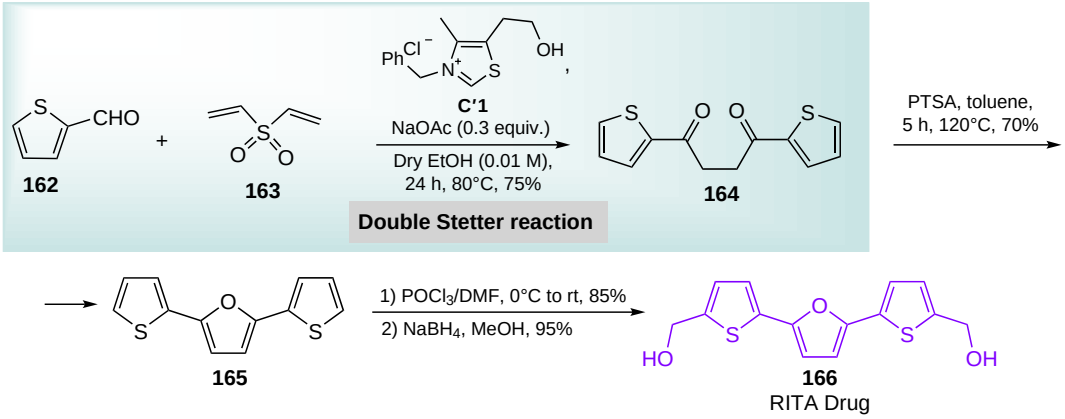
Scheme 35



salt **146** in 90% yield over two steps (see Scheme 34). After that, two different approaches were followed. According to the first approach, the intermediate **146** underwent the Wittig reaction with ethyl glyoxalate **147** to give cinnamate, which was then converted into 2-aminocinnamate **152** by the reduction of the nitro group. In the second approach, phosphonium salt **146** reacted with glyoxalamide **148** and Boc_2O to form the (*Z*)-cinnamamide intermediate **149**, which was converted into compound **150** and after several steps, compound **150** delivered (*E*)-cinnamamide intermediate **152**. Then, intermediate **152** reacted with aldehyde **153** to form an aldimine, which was then converted into substituted indole intermediate **154** (80%) through an intramolecular CN-catalyzed Stetter reaction. Finally, *via* several steps, compound **154** gave rise to rucaparib **157**. The modified synthetic approach to rucaparib involving the key Heck reaction and Stetter reaction reported in the previous study[133] was also mentioned. In the follow-up study,[135] a scalable method was described for synthesizing rucaparib using commercially available starting materials, methyl 5-fluoro-2-methyl-3-nitrobenzoate **145** and 4-cyanobenzaldehyde **155** (see Scheme 34). Compound **145** reacted with *N*,*N*-dimethylformamide dimethyl acetal (DMF · DMA) to form an enamine, which underwent the Strecker reaction with TMSCN to give an α-aminonitrile **151** (75% yield). Next, intermediate **151** was transformed into an *E*-isomer of 2-amino-cinnamonitrile **152** followed by oxidation with *meta*-chloroperoxybenzoic acid (*m*CPBA), K_2CO_3-induced Cope elimination, and reduction with Zn/AcOH. Then, compounds **152** and **155** fused in the presence of $TiCl_4$ produced the corresponding aldimine, which subsequently underwent intramolecular CN-catalyzed imino-Stetter reaction to give indole-3-acetonitrile **156** in 92% yield. After that, compound **156** was transformed into rucaparib **157** *via* several steps. The second-generation synthesis of rucaparib through the Heck reaction offers significant advantages, primarily due to its higher overall yield of 59%, a marked improvement over the 27% yield of the first-generation method based on the Heck reaction. This route also involves fewer separation steps, making it more practical and potentially more scalable for industrial production. In addition, the use of well-established reactions, such as the Heck coupling and the cyanide-catalyzed imino-Stetter reaction, enhances the reliability and reproducibility of the process.

In 2024, Seo *et al.*[136] reported the radiosynthesis of [^{18}F] rucaparib **157** based on a novel highly efficient synthesis of its precursor, pinacol boronate, from the commercially available starting materials. The first step was the Heck reaction between methyl 3-amino-5-chloro-2-iodobenzoate **158** and acrylonitrile **34**, yielding the desired (*E*)-2-aminocinnamonitrile **159** (Scheme 35). Then, the reaction between **159** and aldehyde **153** in the presence of titanium (IV) chloride gave aldimine, which underwent the CN-catalyzed imino-Stetter reaction to yield indole-3-acetonitrile **160**. Following the formation of the indole derivative **160**, the nitrile group was chemoselectively reduced with cobalt boride to an amine, affording indoloazepinone while retaining the chlorine group. After that, the Suzuki–Miyaura borylation was performed involvig the halogen substituent at the

Scheme 36



C6-position of the indole to produce the pinacol boronate **161**. The pinacol boronate was then used for the copper-mediated fluorination with ^{18}F, resulting in the formation of [^{18}F]rucaparib **157**.

Reactivation of p53 and induction of tumour cell apoptosis (RITA) is an anticancer agent featuring a 2,4-bonded thiophene-furan-thiophene scaffold with pendant hydroxymethylene moieties. It exerts cytotoxicity by disrupting the oncogenic p53–HDM-2 interaction, leading to p53 activation and apoptosis. In addition, RITA downregulates oncogenic proteins such as Mcl-1 and c-Myc. Notably, its pro-apoptotic activity persists even in p53-deficient contexts, highlighting its broad therapeutic potential.[137–139] In 2024, Murugesh *et al*.[140] reported the synthesis of the RITA drug **166** through a concise and efficient sequence of reactions primarily utilizing a double Stetter reaction. First, the double Stetter reaction between thiophene-2-carboxaldehyde **162** and divinyl sulfone **163** occurred, catalyzed by benzyl thiazolium **C′1** catalyst and sodium acetate in ethanol, to give 1,4-di(thiophen-2-yl)butane-1,4-dione **164** in 75% yield (Scheme 36). The intermediate **164** underwent the Paal-Knorr furan cyclization promoted by *p*-toluenesulfonic acid (PTSA) in boiling toluene to 2,5-di(thiophen-2-yl)furan **165**, which was then subjected to the Vilsmeier–Haack di-formylation with phosphorus oxychloride in DMF to afford dialdehyde. The final reduction of the resulting dialdehyde using sodium borohydride efficiently produced the target molecule RITA **166** in 95% yield.

5. Conclusion

To conclude, the Stetter reaction remains a cornerstone in modern organic synthesis, providing a reliable route to 1,4-dicarbonyl compounds *via N*-heterocyclic carbene catalysis. Its main advantage lies in enabling polarity inversion of carbonyl compounds, allowing efficient C–C bond formation under mild and selective conditions. In this review, recent methodological advancements, mechanistic insights, and the significance of the Stetter reaction in natural product and drug synthesis have been mentioned and explained. Recent innovations have addressed longstanding challenges such as enantioselectivity, substrate scope, and reaction efficiency through the development of chiral NHCs, photochemical protocols, and enzyme catalysis. Environmentally friendly approaches, including water-based and microwave-assisted reactions, demonstrate the potential for scalable and sustainable synthesis. Among its clear advantages are its high atom economy, operational simplicity, and adaptability to sustainable methods such as solvent-free, aqueous, or mechanochemical conditions. These developments have reduced environmental impact while maintaining high selectivity and yield. The introduction of chiral NHC catalysts has also made it possible to access enantioenriched products valuable in the synthesis of pharmaceutical and natural products. However, several challenges persist, such as limited reaction efficiency in the case of aliphatic aldehydes and achieving high enantioselectivity in intermolecular processes. Scale-up issues, catalyst recovery, and the stability of intermediates also restrict its industrial use. Therefore, further mechanistic studies and catalyst optimization are required. Looking forward, the Stetter reaction is expected to benefit from the integration of green technologies such as continuous-flow systems, electrochemical activation, and recyclable catalysts. The design of more tunable chiral NHCs and hybrid organoenzymatic catalysts could address current limitations and open new pathways for asymmetric synthesis. With ongoing innovation in methodology and sustainability, the Stetter reaction will continue to play a vital role in advancing both academic research and industrial chemistry.

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Conflict of interest

The authors declare no conflicts of interest.

6. List of abbreviations

Ac — acetyl,
ACHN — 1,1′-azobis(cyclohexanecarbonitrile),
All — allyl,
ArtiSt — artificial Stetterase,
BACs — bis(amino)cyclopropenylidenes carbenes,
[Bmim]Br — 1-butyl-3-methylimidazolium bromide,
Bn — benzyl,
Bpin — pinacol boronate ester,
B_2pin_2 — bis(pinacolato)diboron,
BTP — 2-bromo-3,3,3-trifluoropropene,
CBA — chiral Brønsted acid,
c-Myc — cellular myelocytomatosis,
DBU — 1,8-diazabicyclo [5.4.0]undec-7-ene,
DCE —1,2-dichloroethane,
DCM — dichloromethane,
DFT — density functional theory,
DIBAL-H — diisobutylaluminium hydride,
DIC — *N*,*N*′-diisopropylcarbodiimide,
Dipp — 2,6-diisopropylphenyl,
DMAP — 4-dimethylaminopyridine,
DMF —*N*,*N*-dimethyl formamide,
DMF · DMA — *N*,*N*-dimethylformamide dimethyl acetal,
DMSO — dimethylsulfoxide,
DMP — Dess-Martin periodinane,
EDCl —1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,
ERK — extracellular signal-regulated kinase,
Fu — furyl,
HAT — hydrogen atom transfer,
HDM-2 — human double minute 2 protein,
HEPES — 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid,
2-HG — 2-hydroxyglutarate,
hSCP — human steroid carrier protein,
IC_{50} — half maximal inhibitory concentration,
IDH1 — isocitrate dehydrogenase 1,
ITHQ — indolotetrahydroquinolizinium,
α-KG — α-ketoglutarate,
LDA — lithium diisopropylamide,
LiHMDS — lithium bis(trimethylsilyl)amide,
MBnThz — maleimide *N*-benzyl thiazolium salt,
Mcl-1 — induced myeloid leukemia cell differentiation protein,
mCPBA — *meta*-chloroperoxybenzoic acid,
MD — molecular dynamics,
Mes — mesityl,
MOMCl — methoxymethyl chloride,
MS — molecular sieves,
MTBE — methyl *tert*-butyl ether,
MW — microwave irradiation,
Naph — naphthyl,
NBS — *N*-bromosuccinimide,
NHC — *N*-heterocyclic carbenes,

P53 — tumour protein p53,
PARP — poly(ADP-ribose) polymerase inhibitor,
PC — photocatalyst,
Pd_2dba_3 — tris(dibenzyllideneacetone)palladium,
*pf*BAL — *Pseudomonas fluorescens* benzaldehyde lyase,
PMB — *p*-methoxybenzyl,
p-QMs — *p*-quinonemethides,
PTSA — *p*-toluenesulfonic acid,
p-TsCl — *p*-toluenesulfonyl chloride,
Py — pyridyl,
RITA — reactivation of p53 and induction of tumour cell apoptosis,
SCP — steroid carrier protein,
SEM — 2-(trimethylsilyl)ethoxymethyl,
SNi — substitution nucleophilic internal,
Sphos — 2-dicyclohexy[phosphino-2′,6′-dimethoxybiphenyl,
TFA — trifluoroacetic acid,
TBADT — tetrabutylammonium decatungstate,
TBDPS — *tert*-butyldiphenylsilyl,
TBS — *tert*-butyldimethylsilyl,
Tf — triflate (trifluoromethanesulfonyl),
TFE — trifluoroethanol,
Th — thienyl,
ThDP —— thiamine diphosphate,
TMS — trimethylsilyl,
TTSCP — *Thermus thermophilus* steroid carrier protein,
%Vbur — percentage buried volume,
Xphos — 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbi phenyl.

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