Review

A Comprehensive Review on Benzofuran Synthesis Featuring Innovative and Catalytic Strategies

Aqsa Mushtaq, Ameer Fawad Zahoor,* Sajjad Ahmad, Muhammad Jawwad Saif, Atta ul Haq, Samreen Gul Khan, Aamal A. Al-Mutairi, Ali Irfan,* Sami A. Al-Hussain, and Magdi E. A. Zaki*

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Benzofurans have intrigued both pharmaceutical researchers and chemists owing to the medicinal usage of their derivatives against copious disease-causing agents (i.e., bacteria, viruses, and tumors). These heterocyclic scaffolds are pervasively encountered in a number of natural products and drugs. The ever-increasing utilization of benzofuran derivatives as pharmaceutical agents persuaded the chemists to devise novel and facile methodological approaches to assemble the biologically potent benzofuran nucleus. This review summarizes the current developments regarding the innovative synthetic routes and catalytic strategies to procure the synthesis of benzofuran heterocycles with their corresponding mechanistic details, reported by several research groups during 2021−2023.
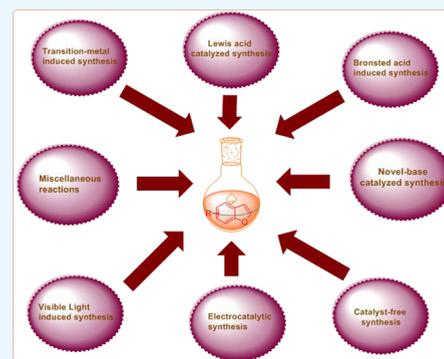
1. INTRODUCTION

Heterocycles are the main components of most of the biologically active compounds.[1] Benzofuran is one of the significant heterocyclic scaffolds, constituting the structural framework of medicinally important organic compounds. A fused benzene ring with a furan core is collectively named as "benzofuran", which is also written as benzo(b)furan. In 1870, Perkin was the first chemist to synthesize the benzofuran ring.[2] Since then, this heterocyclic ring has found numerous applications in the diverse fields of daily life. To date, various benzofuran derivatives have been synthesized which are known to play an efficacious role in medicinal, agricultural, and synthetic chemistry.[3,4] The general structure of the benzofuran heterocycle is illustrated in Figure 1.
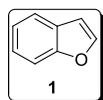
Figure 1. Structural framework of the benzofuran core.

Benzofuran derivatives have been found to be active against bacterial,[5−9] viral,[10,11] inflammatory,[12] and protozoal diseases.[13] For example, diabetes,[14] HIV, tuberculosis,[15] epilepsy,[16] and Alzheimer's disease[17] are some of the most common and widely occurring diseases, against which benzofuran derivatives have been known to play a therapeutic role. In addition, these are effective against a variety of cancers[18−21] and are also employed

as efficient pain killers.[22,23] They also act as efficient enzyme inhibitors, i.e., carbonic anhydrase,[24,25] tyrosinase,[26] topoisomerase I,[27] farnesyl transferase,[28] LSD1 (lysine specific demethylase 1),[29] and histamine receptor inibitors.[30] Furthermore, benzofuran derivatives are also widely harnessed in the preparation of different polymers, i.e., polyamides, polyarylates, polybenzimidazoles, and polyesters.[31,32] They have also found applications in the synthesis of several dyes including dye-sensitized solar cells and industrial dyes.[33,34]

The synthesis of natural products has gained huge importance owing to its significant impact in medicinal chemistry.[35] Most of the naturally occurring organic compounds are embodied with benzofuran heterocycles, particularly the *Moraceae* family[36] and furocoumarins. For example, *Mori cortex radicis* (the root of a few *Morus alba* L.) is used against diabetes and to treat constipation as well.[37−39] Similarly, the noteworthy members of the furocoumarin class, i.e., angelicin **2**, psoralen **4**, and 8-methoxypsoralen **3**, are used in the treatment of skin diseases (psoriasis).[40−43] Another benzofuran-based natural product, i.e., coumestrol **5**, is responsible for estrogenic activity[44] (Figure 2).

Likewise, benzofuran-endowed clinically acknowledged drugs include dronedarone **6** and amiodarone **7**, which inhibit the fast
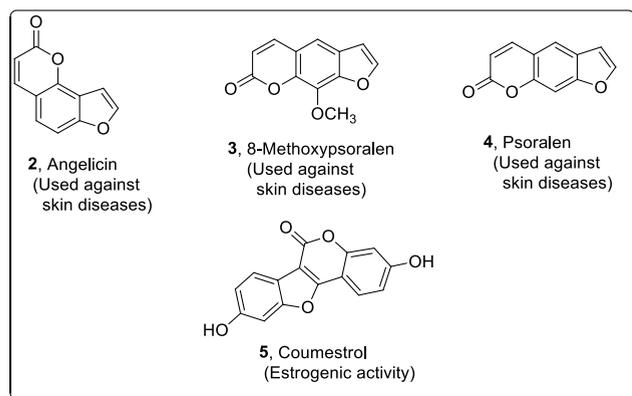
Figure 2. Structures of some biologically active naturally occurring organic compounds incorporated with a benzofuran nucleus.

rhythm of the heart. Benzbromarone **8** is another benzofuran-based drug, used for the treatment of gout. Similarly, saprisartan **9** is used to control high blood pressure[45] (Figure 3).

Considering the medicinal applications of benzofuran derivatives, several methods are reported each year contributing toward their synthesis.[46−54] Most common methods include the reaction of salicylaldehyde with ethylchloroacetate[47]/ethyl-bromoacetate[48−50] or with α-haloketone[51]/acetone.[52] Earlier methods also involved the treatment of hydroxy-substituted acetophenones/halogen-substituted acetophenones with ketones to attain the synthesis of benzofuran heterocycles.[53,54]

Many review articles covering the versatile synthetic approaches for benzofuran synthesis have been published by different research groups.[55,56] Bhargava et al. in 2017 and later Miao et al. in 2019 presented reviews on the synthetic pathways toward the synthesis of medicinally important benzofurans and their derivatives.[57,58] Recently, in mid-2022, another review reporting the biological applications and synthetic strategies to achieve benzofurans was published by Dwarakanath and Gaonkar.[59] Since then, there has been a lot of advancement in the development of novel and efficient synthetic strategies to obtain benzofuran derivatives. This review provides an overview

of all the novel and innovative protocols contributing toward the synthesis of a benzofuran nucleus along with their mechanistic details, reported during 2021−2023.

2. PRECEDENTED APPROACHES

2.1. Benzofuran Synthesis via Transition-Metal-Induced Catalysis.
Transition metals are of irresistible

Scheme 1. Synthesis of Benzofuran Derivatives 11 by Using a Copper-Based Catalyst
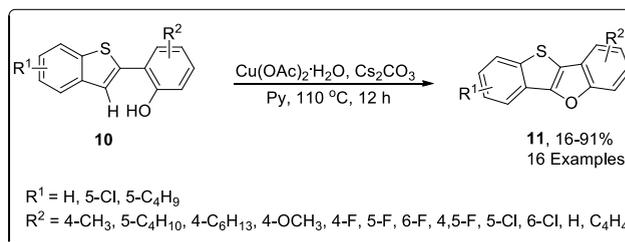
significance, as they are used to catalyze a number of organic reactions, thus resulting in the synthesis of numerous organic compounds. They have also found considerable importance regarding the construction of a benzofuran nucleus. Isolated as well as bimetallic catalytic systems have been reported to construct a benzofuran core. This category involves the utilization of individual transition metals and their salts as catalytic systems for benzofuran synthesis.

2.1.1. Benzofuran Synthesis via Copper-Based Catalyst. Benzofuran derivatives containing a thiophene ring, i.e., benzothieno[3,2-*b*]benzothiophene (BTBT), are known to play a crucial role in the buildout of highly efficient organic photovoltaics. They are efficiently utilized for the construction of field-effect transistors along with other photoelectronic devices.[60] Based on the utilization of BTBT in the framework of these optical devices, various thiophene-substituted benzofuran derivatives have been synthesized by researchers, namely BTBF and BFBF.[61,62] Being persuaded by the earlier reported
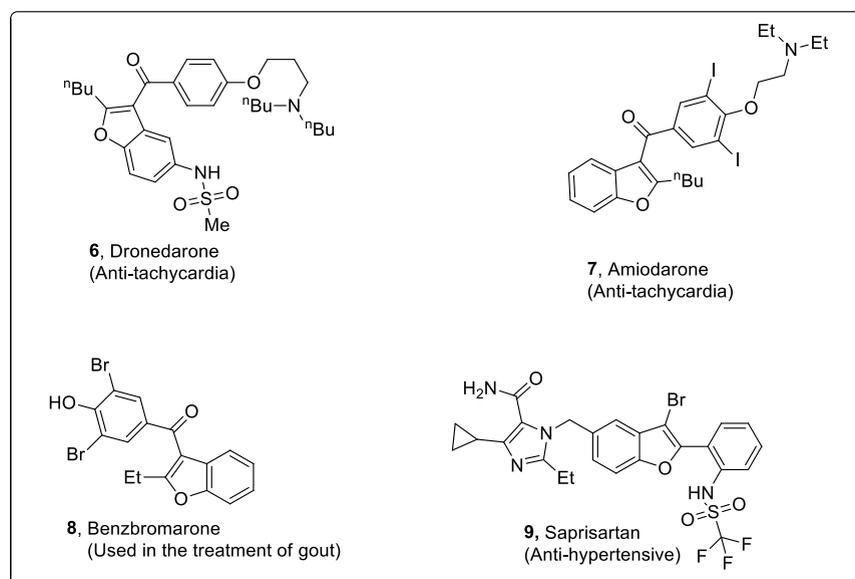
Figure 3. Structures of some clinically acknowledged drugs incorporated with a benzofuran nucleus.
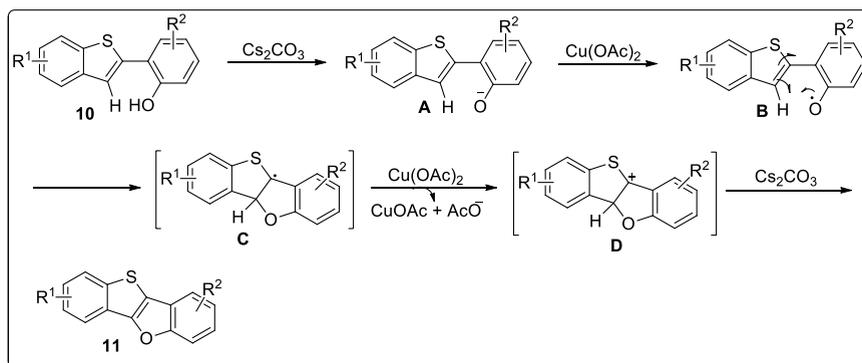
Figure 4. Proposed mechanism for the synthesis of benzofuran derivatives **11** by using a copper-based catalyst.

Scheme 2. Synthesis of Benzofuran Derivatives 14 by Using Copper-Based Catalyst
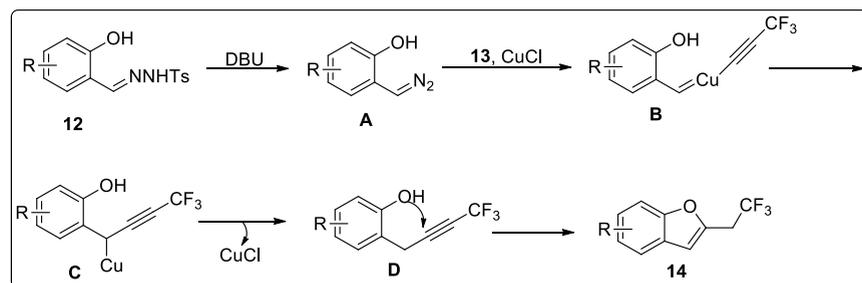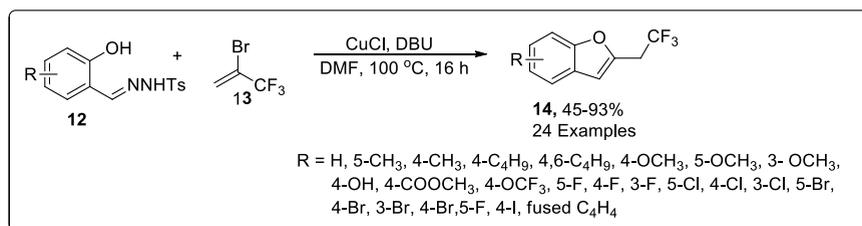
Figure 5. Proposed mechanism for the synthesis of benzofuran derivatives **14** by using copper-based catalyst.

Scheme 3. Synthesis of Benzofuran Derivatives 18 by Using Copper-Based Catalyst
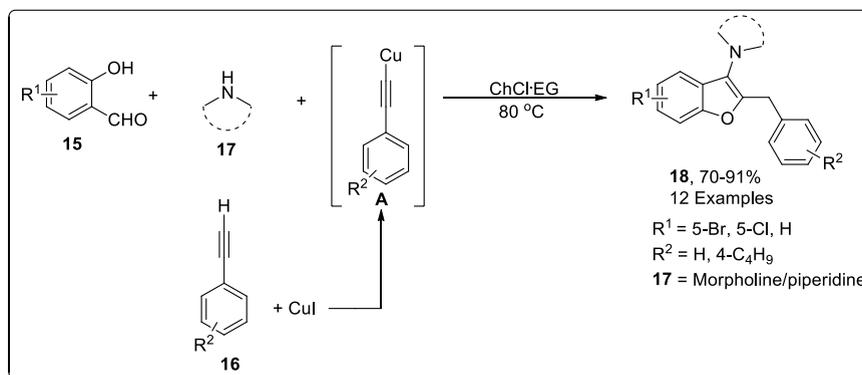
work in this field, Ai et al.[63] in 2021 carried out the O−H/C−H coupling reaction by intramolecular dehydrogenation that resulted in high yields of target molecules. For this purpose, benzothiophene derivative **10** was made to react with the copper catalyst in the presence of cesium carbonate (acting as base) and pyridine (as solvent) (Scheme 1). The reaction mechanism was proposed to initiate with the abstraction of a proton, followed by radical transfer between benzothiophene derivative **10** and a Cu

catalyst to generate intermediate **B**. The resulting intermediate was then subjected to cyclization, oxidation (via copper acetate), and deprotonation (by using base) to synthesize benzofuran derivatives **11** (Figure 4). This established novel synthetic route was also employed toward the gram-scale synthesis of target molecules.

Owing to the significance of copper-based catalysts in several organic transformations,[64,65] Weng et al. also proposed a novel

Scheme 4. Synthesis of Benzofuran Derivatives 19 Using Copper-Based Catalyst

R = H, 5-NO$_2$, 5-Br, 5-F, 5-CH$_3$, 4-Cl, 4-CH$_3$, 3-CH$_3$, 3-OCH$_3$, 3-OC$_2$H$_5$
17 = Piperidine, tetrahydroquinoline, morpholine, pyrrolidine, diethylamine, diallylamine, N-methylcyclohexanamine
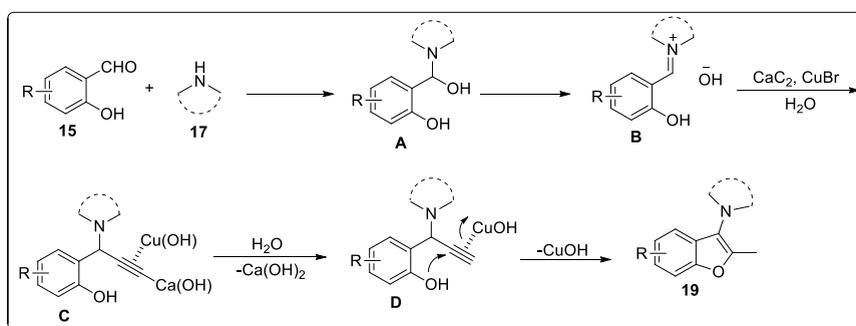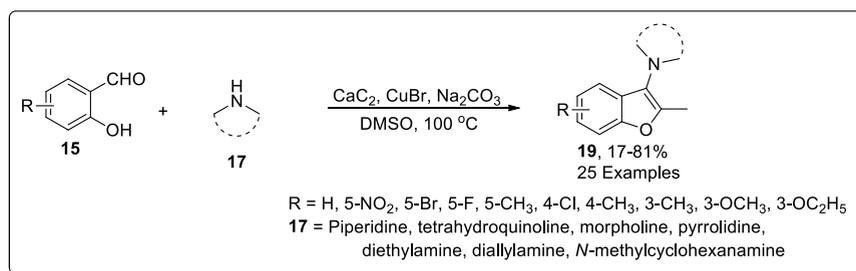
Figure 6. Proposed mechanism for the synthesis of benzofuran derivatives **19** by using a copper-based catalyst.

Scheme 5. Synthesis of Benzofuran Derivatives 22 by Using Palladium-Based Catalyst

R^1 = H, 4-CH$_3$, 4-OCH$_3$, 4-CF$_3$, 4-Cl, 3-Cl, 2-Cl
R^2 = H, 3,5-di-t-butyl, 4,N,N-diethyl, 5-Cl
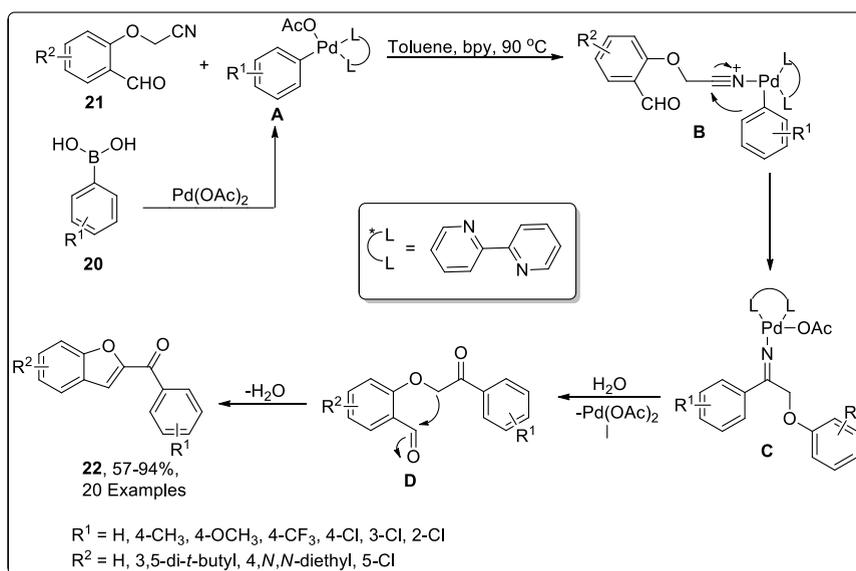
Scheme 6. Synthesis of Benzofuran Derivatives 28 by Using Palladium-Based Catalyst

R^1 = H, 5-CH$_3$, 4-CH$_3$, 5-F, 4-F, 4-Cl, 5-Cl, 5-NO$_2$, 5-CF$_3$, 5-CN, 6-Cl
R^2 = H, CH$_3$, CH$_2$C$_6$H$_5$, Boc, Ts
R^3 = CH$_3$, C$_6$H$_5$
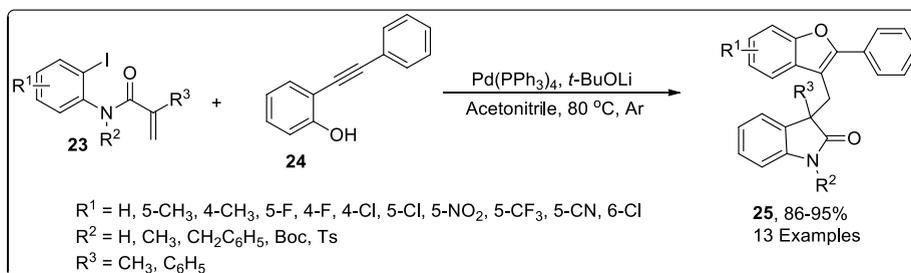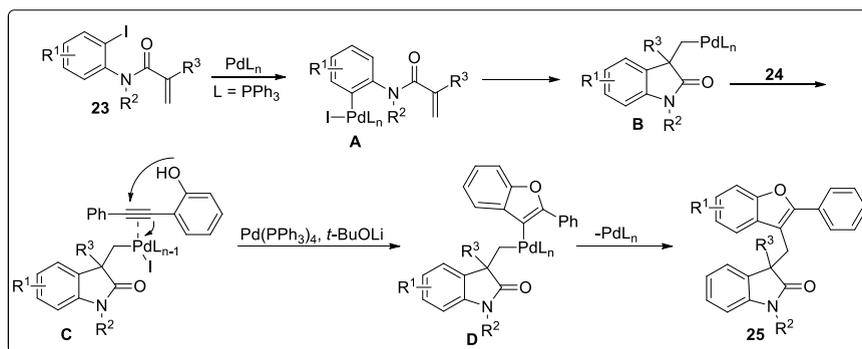
Figure 7. Proposed mechanism for the synthesis of benzofuran derivatives **25** by using a palladium-based catalyst.

Scheme 7. Synthesis of Benzofuran Derivatives 28 by Using Palladium-Based Catalyst
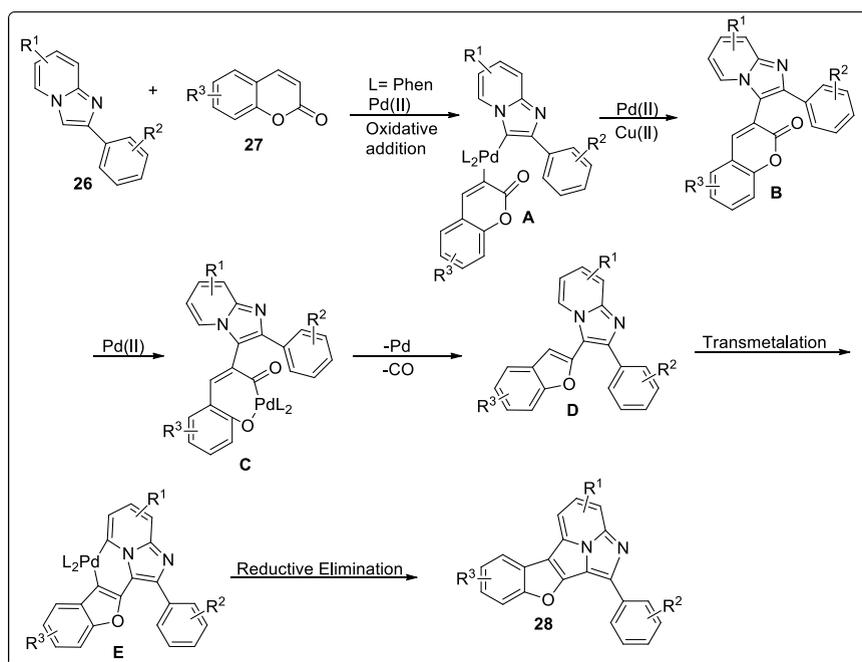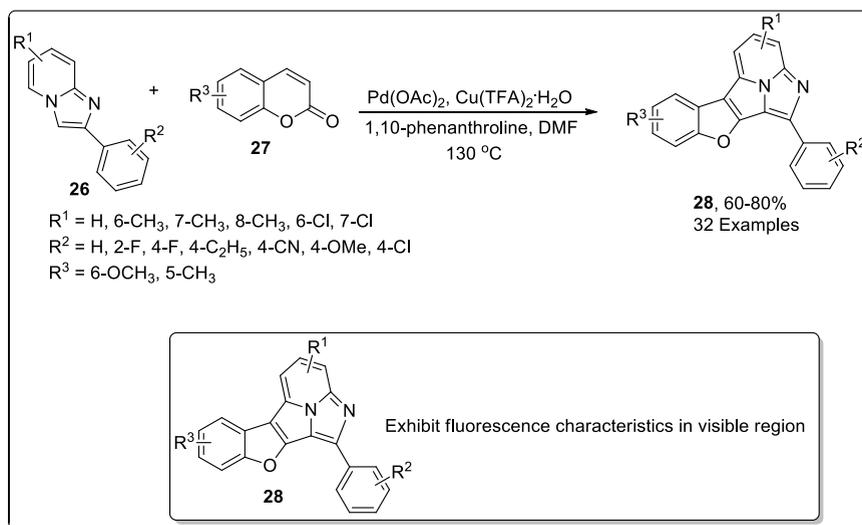
Figure 8. Proposed mechanism for the synthesis of benzofuran derivatives **28** by using a palladium-based catalyst.

Scheme 8. Synthesis of Benzofuran Derivatives 31 by Using Palladium-Based Catalyst
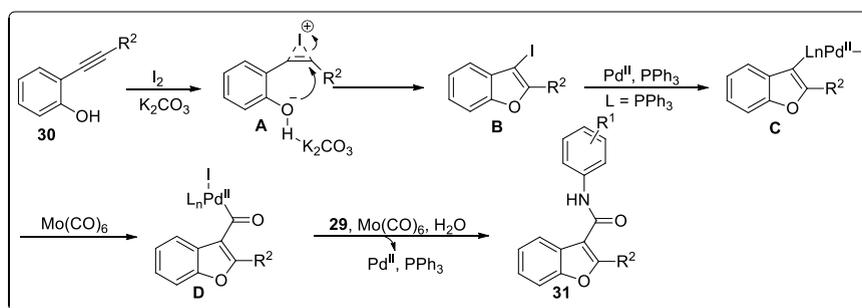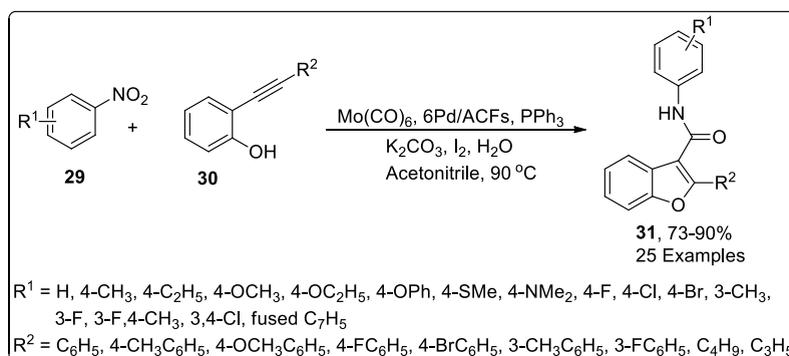
Figure 9. Proposed mechanism for the synthesis of benzofuran derivatives **31** by using a palladium-based catalyst.

Scheme 9. Synthesis of Benzofuran Derivatives 34 by Using Palladium-Based Catalyst
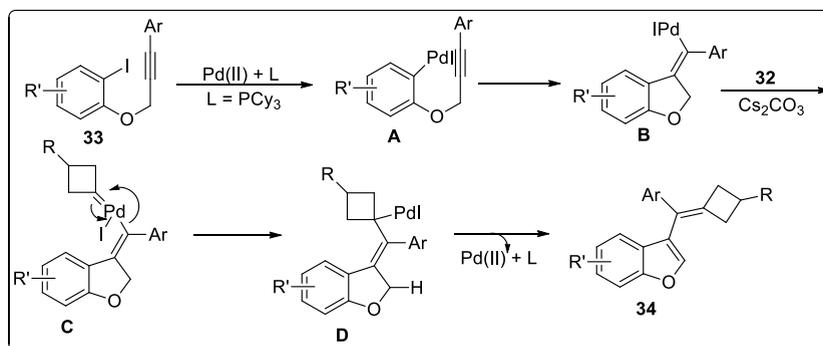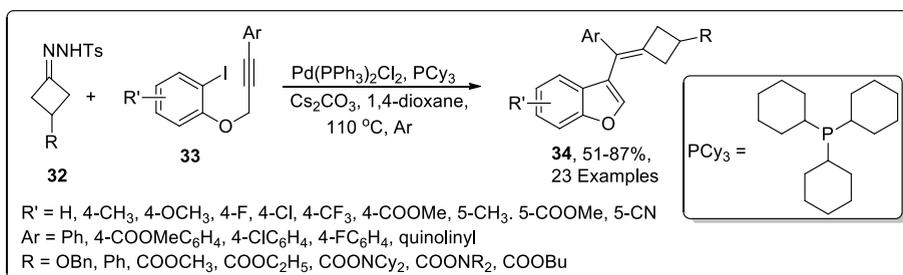
Figure 10. Proposed mechanism for the synthesis of benzofuran derivatives **34** by using a palladium-based catalyst.

copper-catalyzed methodology to obtain benzofuran derivatives with their gram-scale synthesis.[66] They treated substituted salicylaldehyde-derived Schiff bases **12** and substituted alkenes **13** by utilizing copper chloride as a catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in dimethylformamide solvent, thus attaining trifluoroethyl-substituted

benzofuran derivatives **14** in efficient yields (45−93%) (Scheme 2). The reaction mechanism was presumed to proceed by the coupling of intermediate **A** (obtained by treating **12** with base) with copper acetylide (achieved by the treatment of substituted alkenes **13** with CuCl) to generate intermediate **B**. The intermediate **B** then underwent reductive elimination followed

Scheme 10. Synthesis of Benzofuran Derivatives 38 and 39 by Using Pd–Cu-Based Catalyst

R = H, 4-COMe, 4-NO₂, 4,6-Br, 4,6-Cl, 4-CH₃,6-Cl,

38, 81-90%
7 Examples

39, 84-91%
8 Examples

36   **37**

39a   **39b**   **39c**

Exhibited 64-65% chorismate mutase in-vitro inhibition at 30 μM
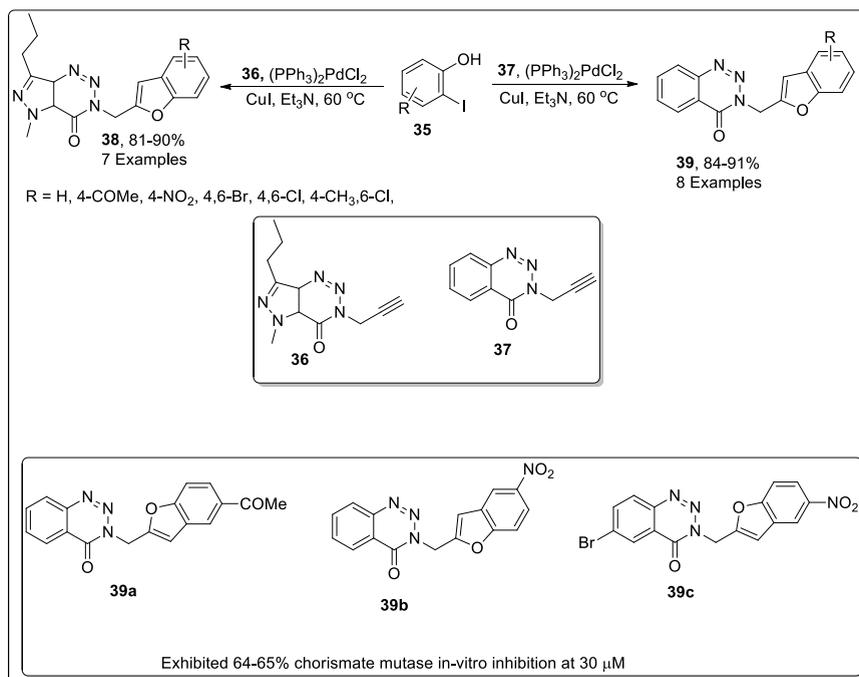
Scheme 11. Synthesis of Benzofuran Derivatives 41 by Using Ni-Based Catalyst

Ni(OTf)₂, 1,10-Phen
Zinc powder, MeCN
N₂, 110 °C

41, 23-89%
20 Examples

i. Demetallization
ii. Dehydration

Ni(OTf)₂, 1,10-Phen
Zinc powder

ZnX₂

A   **B**   **C**

R^1 = H, 5-CH₃, 5-C₂H₅, 5-C₄H₉, 5-F, 4-Cl, 5-Cl, 5,6-CH₃, 5-Br, 4-Br, fused C₄H₄
R^2 = H, CH₃
R^3 = H, 4-CH₃, 4-OCH₃, 4-Cl, 4-F, 3,4-Cl, 2-Cl, 2-CH₃, fused C₄H₄
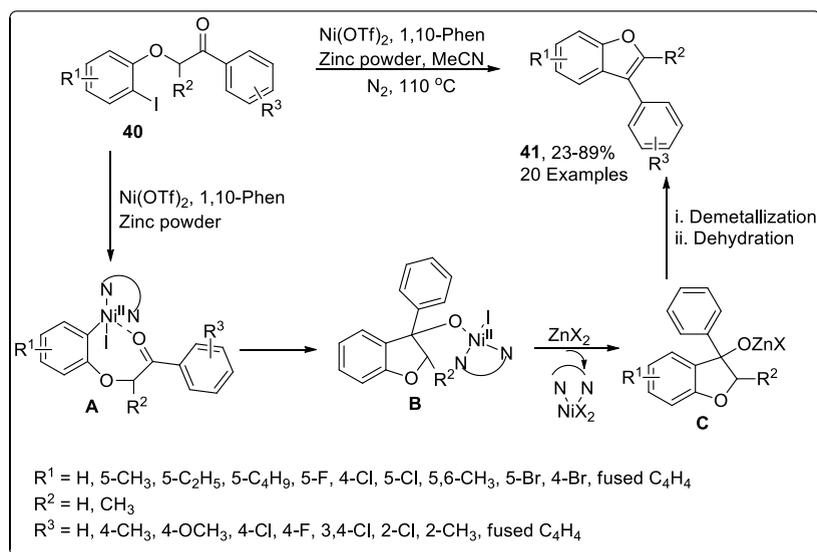
Scheme 12. Synthesis of Benzofuran Derivatives 47 by Using Rh-Based Catalyst

CpRh, tetrachloroethane
80 °C, 18 h

42 + **43**

44, 30-80%
7 Examples

R = 2-OCH₃, 3-Cl, 3-Br, 3-n-C₄H₉, 3-C₆H₅, 3-———TIPS, 2-CH₃
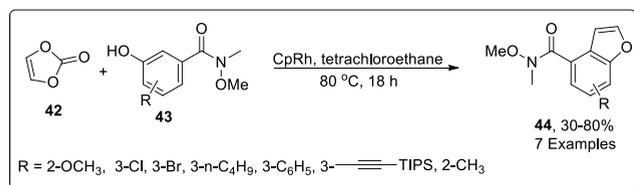
by acidification and rearrangement to prepare benzofuran derivatives **14** (Figure 5).

Contributing to the development of novel methods to obtain a benzofuran ring, Abtahi and Tavakol[67] reported a green and environmentally benign approach. They carried out a one-pot synthesis by reacting different *o*-hydroxy aldehydes **15**, amines **17**, and diversely substituted alkynes **16** in the presence of copper iodide (acting as a catalyst). Moreover, they furnished the synthesis of benzofuran derivatives by availing the use of eco-friendly deep eutectic solvent (DES), i.e., choline chloride-ethylene glycol (ChCl.EG). DESs are known for their ability to stabilize the polar intermediates as well for speedy trans-formations. The chloride ion in DES also entails the ability to behave as a weak base. A number of different benzofuran derivatives were synthesized by using these catalyst and solvent conditions in good to excellent yields (70−91%). It was observed that high yields of target molecules were attained by employing electron-donating substituted salicylaldehydes as precursors. The reaction mechanism was proposed to proceed
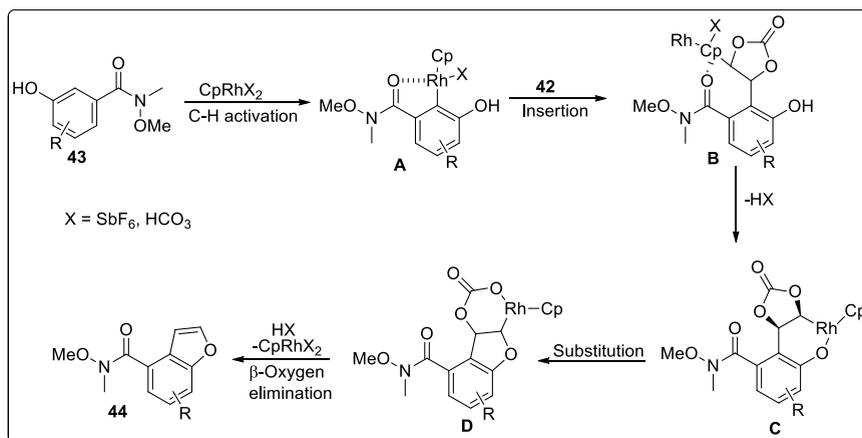
Figure 11. Proposed mechanism for the synthesis of benzofuran derivatives **44** by using Rh-based catalyst.

Scheme 13. Synthesis of Benzofuran Derivatives 47 by Using Rh-Based Catalyst

R^1 = H, 5-F, 3-F, 4-CH$_3$
R^2 = CH$_3$, C$_2$H$_5$, C$_6$H$_{13}$, CH$_2$Ph
R^3 = H, 4-C$_4$H$_9$, 4-OCH$_3$, thiophenyl
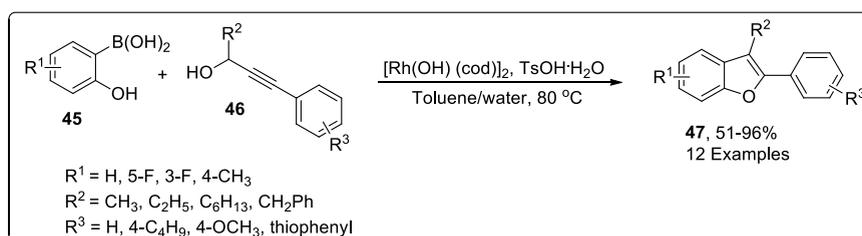
Scheme 14. Synthesis of Benzofuran Derivatives 53 by Using Rh-Based Catalyst

R^1 = H, 2-CH$_3$, 2-Cl, 3-CH$_3$, 3-Cl, 3-NO$_2$, 4-CH$_3$, 4-C$_4$H$_9$, 4-Br, 4-C$_6$H$_5$, 4-COOCH$_3$
R^2 = n-C$_3$H$_7$, n-C$_5$H$_{11}$, n-C$_6$H$_{13}$, C$_6$H$_5$, 4-CH$_3$C$_6$H$_4$, 4-FC$_6$H$_4$
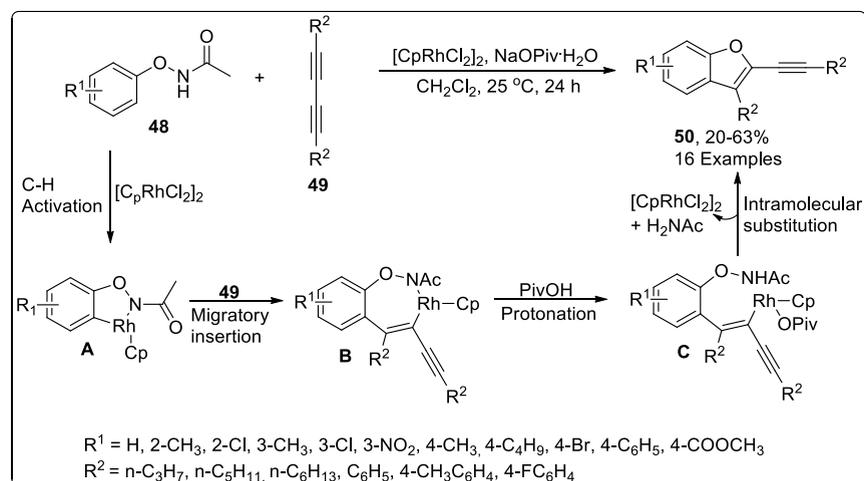
Scheme 15. Synthesis of Benzofuran Derivatives 53 by Using Au- and Ag-Based Catalysts

R^1 = CH$_3$, C$_2$H$_5$
R^2 = CH$_3$, C$_2$H$_5$, C$_3$H$_5$, C$_6$H$_5$, 4-CH$_3$C$_6$H$_4$, 4-OCH$_3$C$_6$H$_4$, 4-ClC$_6$H$_4$
4-BrC$_6$H$_4$, 4-C$_4$H$_9$-C$_6$H$_4$, 4-COOCH$_3$C$_6$H$_4$, 3,5-CH$_3$C$_6$H$_3$, 2-CH$_3$
C$_6$H$_4$,3-CH$_3$C$_6$H$_4$, thiophenyl, naphthyl
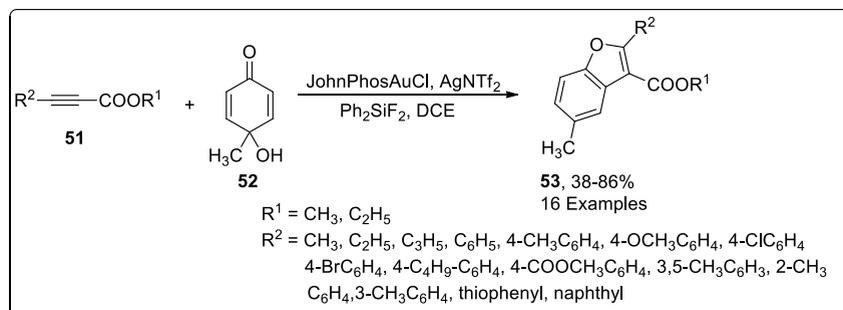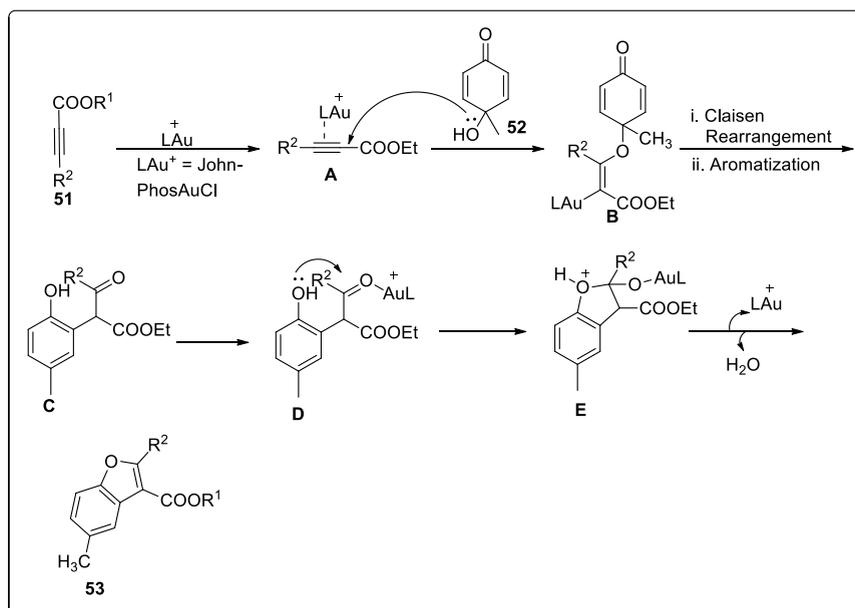
Figure 12. Proposed mechanism for the synthesis of benzofuran derivatives **53** by using Au- and Ag-based catalysts.

Scheme 16. Synthesis of Biologically Active Benzofuran Derivatives 55
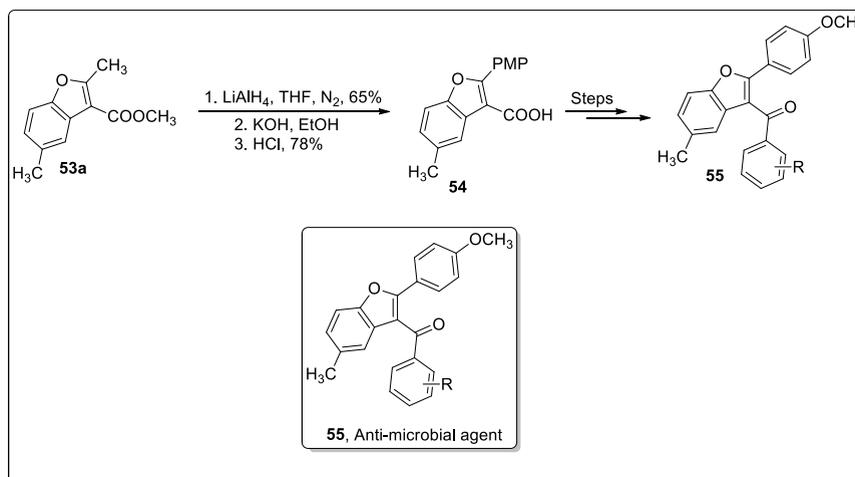
via iminium ion formation, followed by the attack of copper acetylide **A** on the iminium ion. The intermediate **A** was then transformed to generate benzofuran derivatives **18** as a result of intramolecular cyclization and isomerization (Scheme 3).

In 2021, Ma et al.[68] reported another efficient one-pot strategy yielding benzofuran derivatives **19** by treating substituted amines **17**, salicylaldehydes **15**, and calcium carbide (used to generate alkynes). The one-pot reaction involved the utilization of copper bromide, sodium carbonate, water, and dimethyl sulfoxide to afford amino-substituted benzofuran skeletons **19** in high yields (Scheme 4). This synthetic protocol is a potential gateway to achieve medicinally essential benzofuran derivatives. The plausible reaction pathway involved the formation of iminium ion **B** that proceeded by the attack of copper acetylide (which was obtained by the hydrolysis of calcium carbide followed by the utilization of cuprous bromide) to generate intermediate **C**. The intermediate **C** then afforded benzofuran derivatives **19** via intramolecular nucleophilic attack and isomerization (Figure 6).

2.1.2. Benzofuran Synthesis via Palladium-Based Catalyst. Palladium metal has been widely employed for the synthesis of various organic compounds[69] as well as for benzofuran derivatives.[70] Luo et al.[71] carried out the synthesis of benzoyl-substituted benzofuran heterocycles **22** by treating aryl boronic acid **20** with 2-(2-formylphenoxy) acetonitriles **21** via palladium acetate-catalyzed reaction. A wide range of substituted reactants were employed in standard reaction conditions [(Pd(OAc)$_2$ (30 mol %) as catalyst, bpy as ligand (30 mol %), toluene as solvent, and at 90 °C] to analyze the substrate scope of this novel synthetic methodology. As a result, a series of substituted benzofurans **22** was attained in moderate to excellent yields (58−94%). The reaction was proposed to move forward via transmetalation, which gave rise to intermediate **A**, followed by the coordination of the nitrile moiety and intramolecular insertion to afford intermediate **C**. The intermediate **C** then underwent subsequent hydrolysis and aldol condensation to yield benzofuran derivatives **22**. Thus, the synthetic approach yielded target molecules by involving Pd-mediated sp−sp^2

Scheme 17. Synthesis of Benzofuran Derivatives 58 and 60 by Using Au- and Ag-Based Catalysts

R^1 = H, 2-CH$_3$, 3-CH$_3$, 5-CH$_3$, 4-CH$_3$, 4-OCH$_3$, 4-Cl, 4-Br, 4-F, 4-C$_4$H$_9$
Ar = C$_6$H$_5$, 4-CH$_3$C$_6$H$_4$, 4-OCH$_3$C$_6$H$_4$, 4-t-butylC$_6$H$_4$, 4-FC$_6$H$_4$,
    3-CH$_3$C$_6$H$_4$, 3-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, thiophenyl, naphthyl

R^1 = 4-Ms, 4-COOMe, 4-Ac, 4-CHO, 4-CF$_3$, 4-CN, 4-NO$_2$, 4-OCH$_3$, 2-CHO, 2-NO$_2$
    2-Br, 3,5-Cl, 3,5-Br, 3,5-OCH$_3$, 4-CHO,5-CH$_3$, 3,4,5-F, 4-NO$_2$-fused C$_4$H$_4$.
    fused C$_4$H$_4$, fused Br-C$_4$H$_4$, fused C$_3$H$_3$N, fused C$_2$H$_2$N$_2$, fused COC$_2$H$_2$O,
    fused COOC$_2$H$_2$, 4-NO$_2$-fused C$_3$H$_3$N
R^2 = Ph, 4-MePh, 4-OMePh, 4-ClPh, 4-BrPh, 4-FPh, 4-CF$_3$Ph, 4-CNPh, Me, ^{n}Bu,
    thiophenyl

Scheme 18. Synthesis of Benzofuran Derivatives 64 by Using Ru-Based Catalyst

R^1 = H, 5-CH$_3$, 5-OBn, 5-Cl, 5-Br, 5-CF$_3$, 5-OH, 5-COOH, 5,6-OCH$_3$, 5-OH,6-CH$_3$
    5-OH,6-Br, 6-F, 6-Cl
R' = C$_6$H$_5$, 4CH$_3$C$_6$H$_4$, 4-OCH$_3$C$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-OCF$_3$C$_6$H$_4$,
    3,4,5-CH$_3$C$_6$H$_2$, 3,4,5-OCH$_3$C$_6$H$_2$
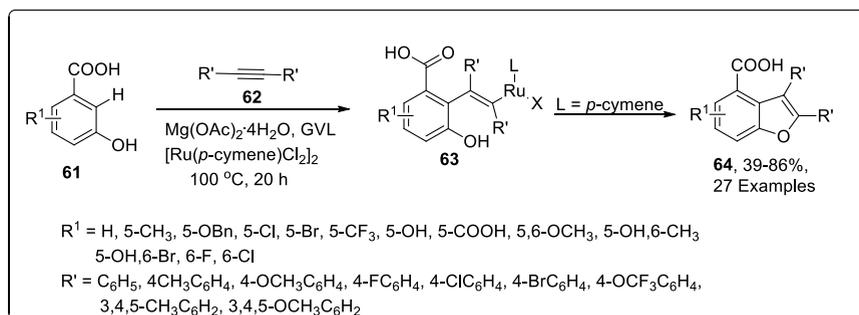
Scheme 19. Synthesis of Diptoindonesin G 68 by Using Ru-Based Catalyst

Diptoindonesin G demonstrate antiproliferative activity by interrupting G2/M phase in acute myeloid leukemia cells
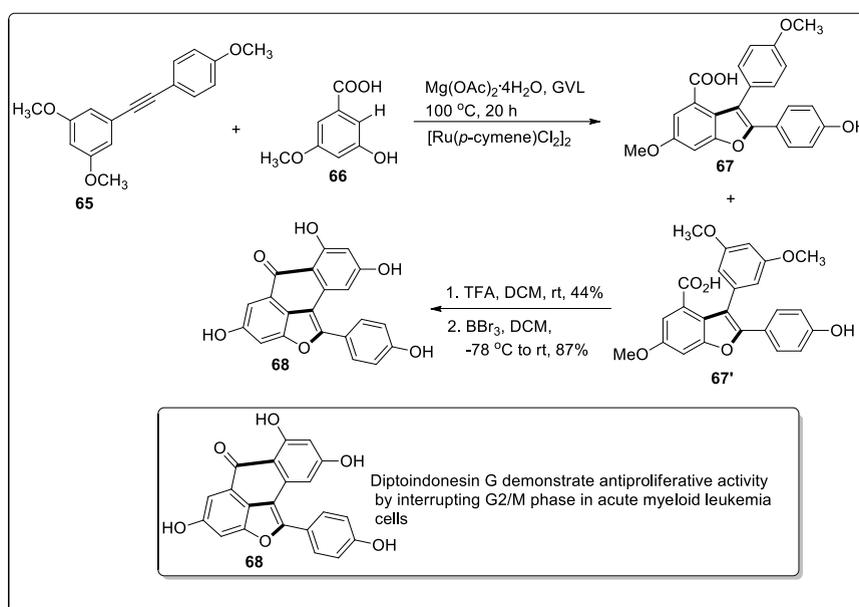
Scheme 20. Synthesis of Benzofuran Derivatives 70 by Using Ru-Based Catalyst
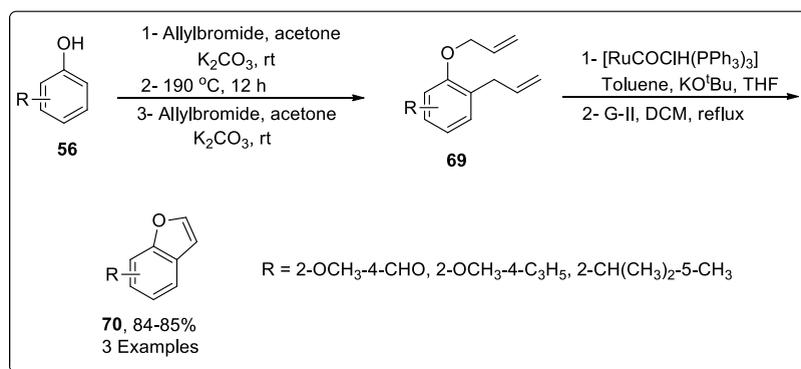
Scheme 21. Synthesis of Phenylpropanoids 72−74 by Using Ru-Based Catalyst
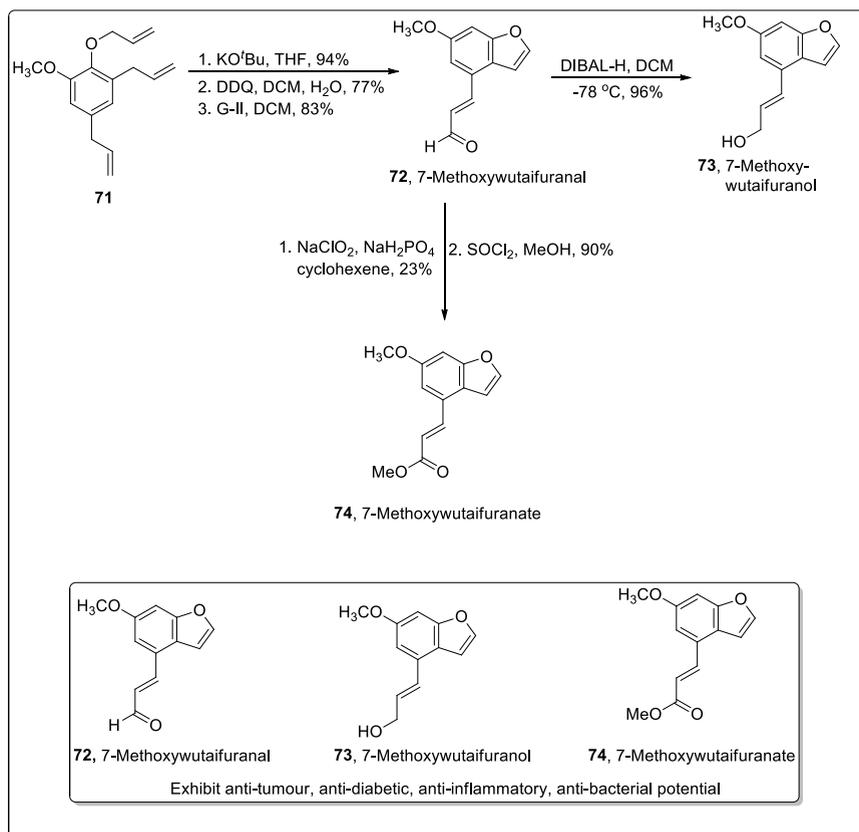
coupling with subsequent intramolecular annulation (Scheme 5).

Another example of palladium-mediated synthesis of benzofuran heterocycles **25** was reported in the same year by Qi et al.[72] They accomplished the ligand-free synthesis of benzofuran derivatives **25** by treating 2-(phenylethynyl)phenol **24** and *N*-(2-iodophenyl)-*N*-methylmethacrylamides **23** utilizing a palladium-tetrakis(triphenylphosphine) catalyst in the presence of lithium *tert*-butoxide base and acetonitrile solvent. In this way, alkenes were subjected to aryl furanylation to synthesize numerous benzofuran derivatives, **25** (Scheme 6). Their synthetic route involved the oxidative addition followed by the cyclization process via an intramolecular Heck reaction to give intermediate **B**. The intermediate **B** then coordinated with **24**, thereby giving intermediate **C**. In the next step, intermediate

C underwent lithium *tert*-butoxide-base-mediated cyclization followed by reductive elimination to construct the benzofuran scaffolds **25** (Figure 7).

In the same year, Semwal et al.[73] proposed the palladium-promoted synthesis of benzofuran derivatives via ring formation reaction between imidazo[1,2-*a*]pyridines **26** and coumarins **27**. They treated coumarins and imidazo[1,2-*a*]pyridines by employing palladium acetate as a catalyst, Cu(OTf)$_2$·H$_2$O as an oxidant, dimethylformamide as solvent, and 1,10-phenanthroline (as an excellent additive and catalyst) to procure benzofuran derivatives (by the removal of CO) in efficient yields (Scheme 7). The reaction mechanism was proposed to proceed via generation of a metal complex as a result of oxidative addition of imidazo-pyridines **26** and coumarins **27**. This step was followed by the reductive elimination, insertion of palladium,

Scheme 22. Synthesis of Benzofuran Derivatives 77 by Using Lewis Acid As a Catalyst

$R' = C_6H_5$, $SiMe_3$, $4-CF_3C_6H_4$
$R^1 = CH_3$, $4-CH_3C_6H_4$
$R^2 = CH_3$, C_3H_6, C_2H_5

Eustifoline D analogues 77(g-i)
Wide medicinal significance
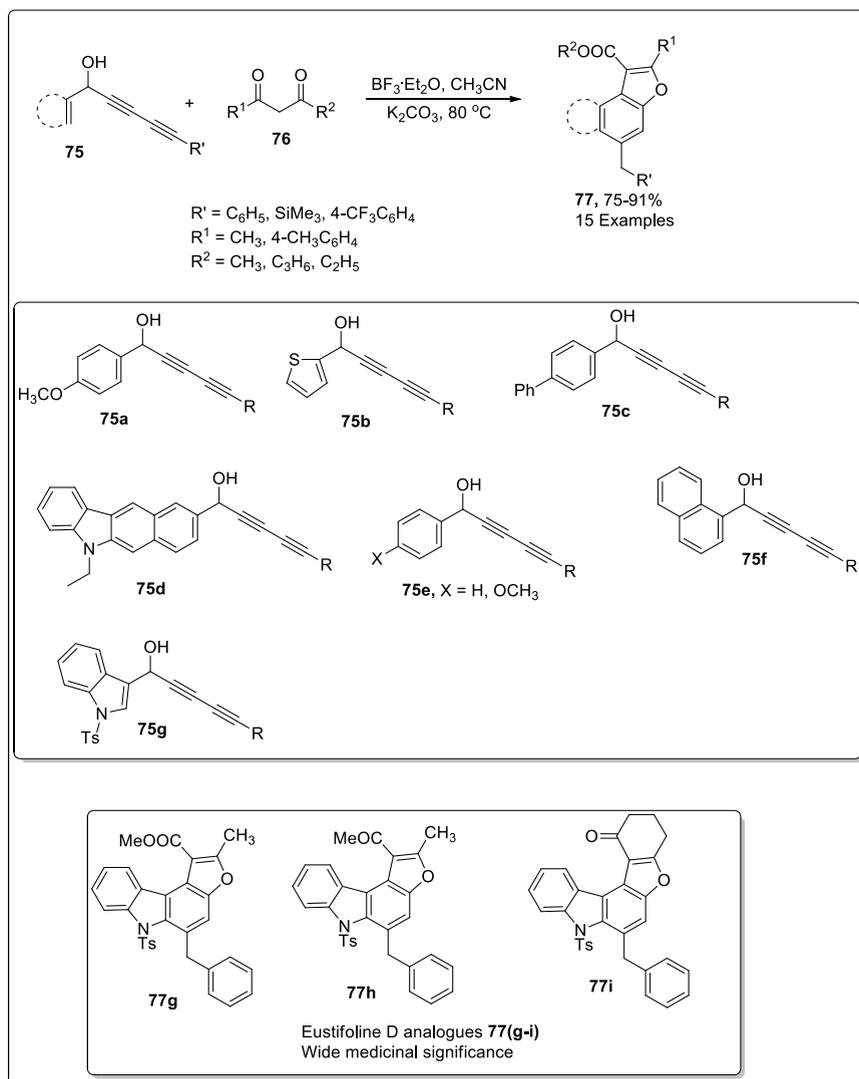
Scheme 23. Synthesis of Benzofuran Derivatives 80 by Using Lewis Acid As a Catalyst

$R^1 = H$, $4-CH_3$, $4-F$, $5-Br$
$R^2 = 4-OCH_3C_6H_4$, $4-COOMeC_6H_4$, $2-BrC_6H_4$, $2-ClC_6H_4$, $4-NO_2C_6H_4$. C_6H_5, $4-CN$, $4-CF_3$, $3-OCH_3$
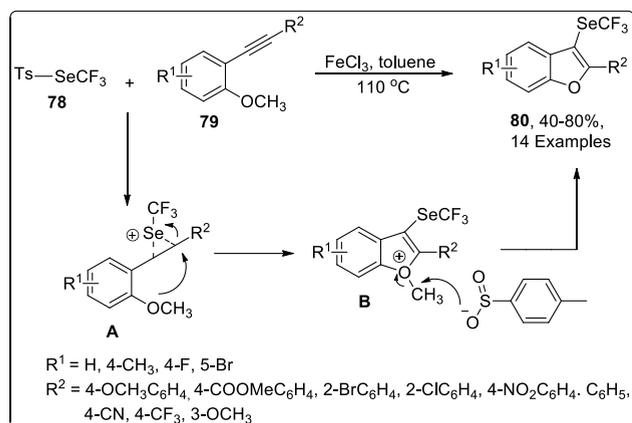
and removal of carbonyl to generate intermediate **D**. Later, the oxidation of palladium was carried out by using copper triflate (oxidant), followed by subsequent electrophilic C−H palladation, which ultimately resulted in benzofuran-based fused

products **28** by undergoing reductive elimination (Figure 8). The synthesized benzofuran derivatives were found to manifest the fluorescence in the visible light range.

Activated carbon fibers are widely exploited in organic reactions due to their efficient resistance against severe chemicals and high temperature. Considering the significance of activated carbon fibers in catalytic systems, Wang et al.[74] reported the use of palladium-linked activated carbon fibers as catalyst to furnish benzofuran derivatives **31**. In this regard, nitroarenes **29** were made to react with *o*-alkynylphenols **30** over a heterogeneous catalytic system (activated carbon fibers sustained palladium) involving triphenylphosphine as an oxidant, molybdenum hexacarbonyl as a carbonyl group substitute and reductant, potassium carbonate as a base, and iodine as an additive in water and acetonitrile. Electron-withdrawing substituents on the phenyl ring diminished the yield of benzofuran derivatives and vice versa (Scheme 8). The reaction strategy involved the preparation of iodonium salt by using iodine followed by (triphenylphosphine-mediated) oxidative addition to generate intermediate **C**. In the next step, insertion of a carbonyl group transformed intermediate **C** to intermediate **D**. The intermediate **D** further carried out the reduction of nitroarenes **29** by using water to generate targeted

Scheme 24. Synthesis of Benzofuran Derivatives 82 and 84 by Using Lewis Acid As Catalyst
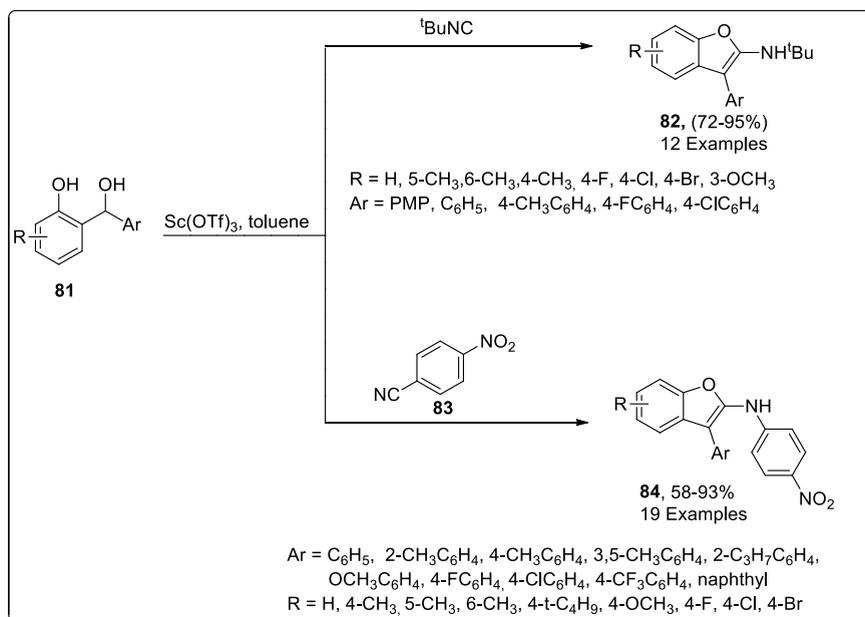
Scheme 25. Synthesis of Benzofuran Derivatives 87 by Using Bronsted Acid As Catalyst
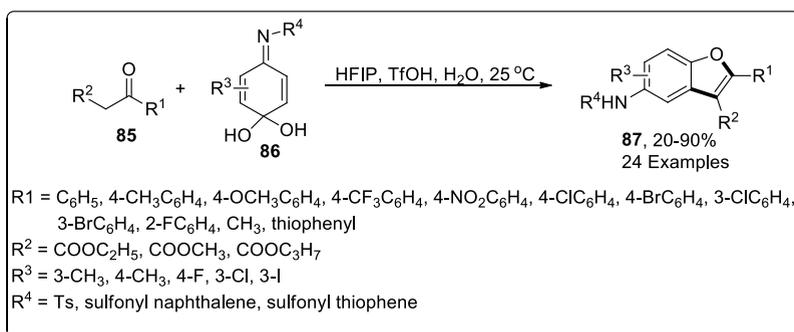
Scheme 26. Synthesis of Benzofuran Derivatives 89 by Using Bronsted Acid As Catalyst
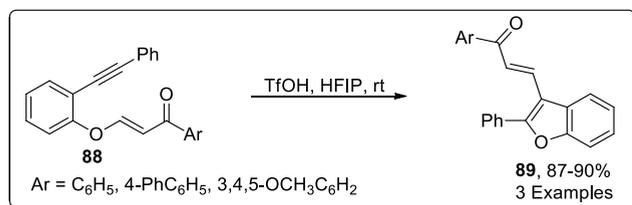
derivatives 31 via intramolecular nucleophilic reaction (Figure 9).

Another example of palladium-catalyzed synthesis of benzofuran derivatives was reported by Sun's[75] group in 2023. In this regard, they treated N-tosylhydrazones 32 (obtained from cyclobutane) and iodobenzene-joined alkynes 33 using bis(triphenylphosphine)palladium(II) dichloride catalyst, PCy_3 (tricyclohexylphosphine), as a ligand in the presence of cesium carbonate base and toluene (as solvent) (Scheme 9). The reaction was initiated with the oxidative addition proceeded by carbopalladation with iodobenzenes 33 to generate intermediate **B**. The intermediate **B** was then made to react with diazocompounds (obtained by cesium carbonate promoted decomposition of N-tosylhydrazones 32) to attain intermediate

C. The obtained intermediate **C** further underwent migratory insertion of Pd-carbene, followed by γ-hydride elimination and cycloaddition reactions to afford dihydrobenzofurans 34 (Figure 10).

2.1.3. Benzofuran Synthesis via Palladium–Copper-Based Catalyst. Considering the utility of Pd- and Cu-catalyzed synthesis of benzofuran heterocycles, the Reddy group[76] in 2022 availed the used of both palladium and copper by employing them as catalysts in Sonogashira coupling reaction between terminal alkynes 36/37 and iodophenols 35, which upon intramolecular cyclization resulted in the synthesis of benzofuran derivatives. In the developed approach, copper iodide was employed as a cocatalyst with the $(PPh_3)PdCl_2$ catalyst in triethyl amine (base and solvent). It was observed that target molecules were not attained by proceeding the reaction without the addition of cocatalyst, i.e., CuI. This methodology resulted in high yields of target molecules (84−91%). The synthesized benzofuran derivatives were then assessed for their activity as antitubercular agents, i.e., chorismate mutase inhibitors (which inhibits the activity of chorismate mutase enzyme in bacterial action). Among the synthesized compounds, benzofuran derivatives 39(a−c) were found to be active against chorismate muatse with 64−65% in vitro inhibition at 30 mM. Thus, these
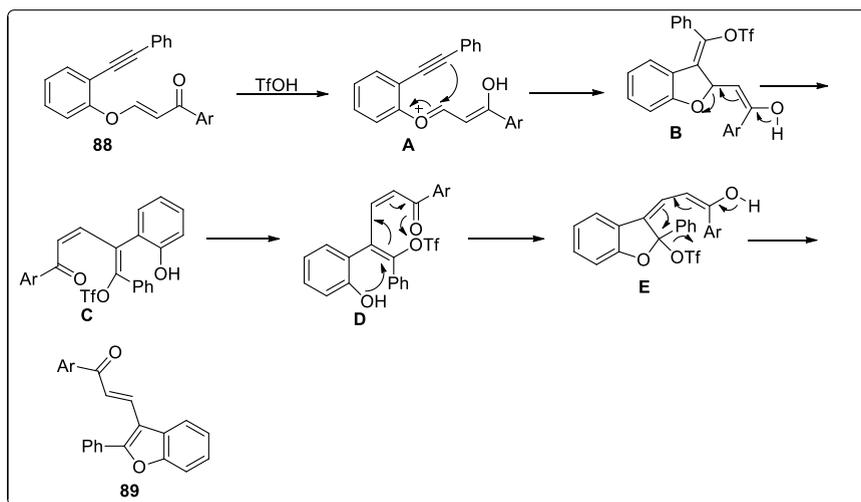
Figure 13. Proposed mechanism for the synthesis of benzofuran derivatives **89** by using Bronsted acid as catalyst.

Scheme 27. Synthesis of Benzofuran Nucleus 92 by Employing Bronsted Acid As Catalyst
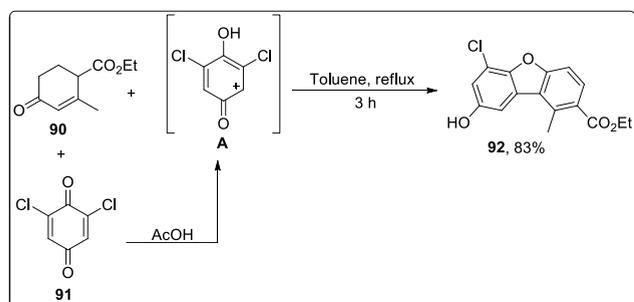
Scheme 29. Synthesis of Benzofuran Derivatives 99 by Using Triethylamine As a Catalyst
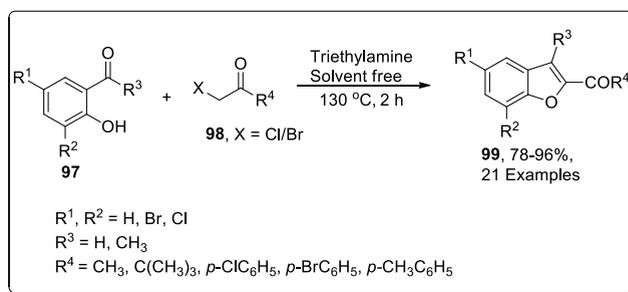
Scheme 28. Visible-Light-Mediated Synthesis of Benzofuran Derivatives 94 and 96
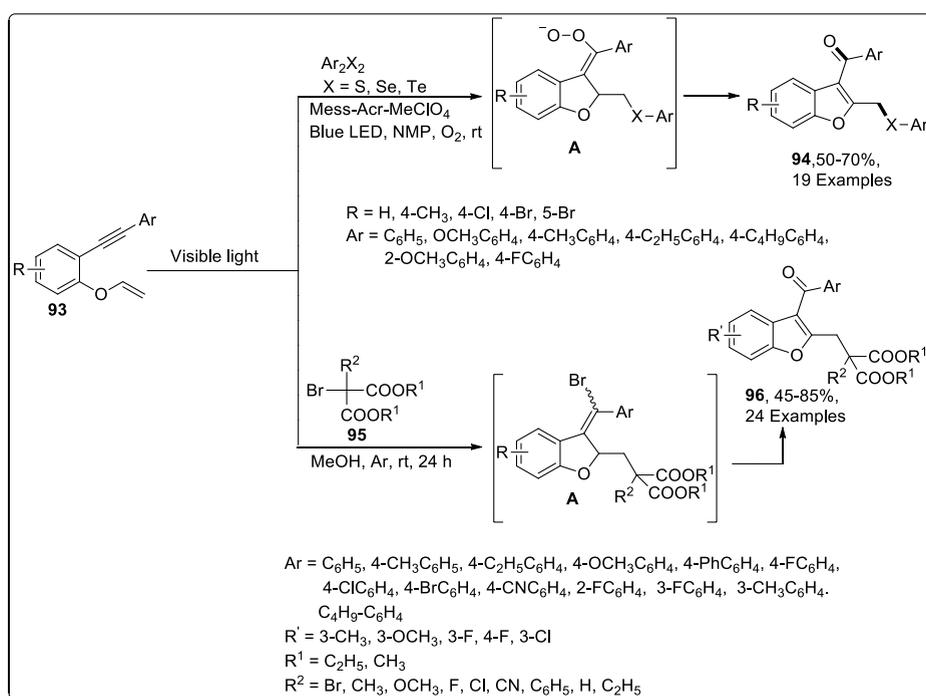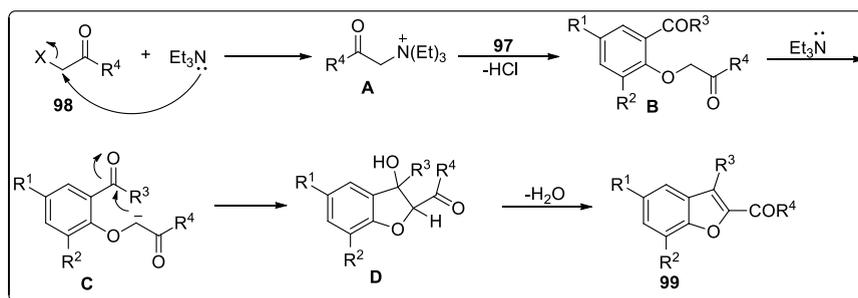
Figure 14. Proposed mechanism for the synthesis of benzofuran derivatives **99** by using triethylamine as a catalyst.

Scheme 30. Synthesis of Benzofuran Derivatives 101 and 5 by Using Potassium *tert*-Butoxide As a Catalyst
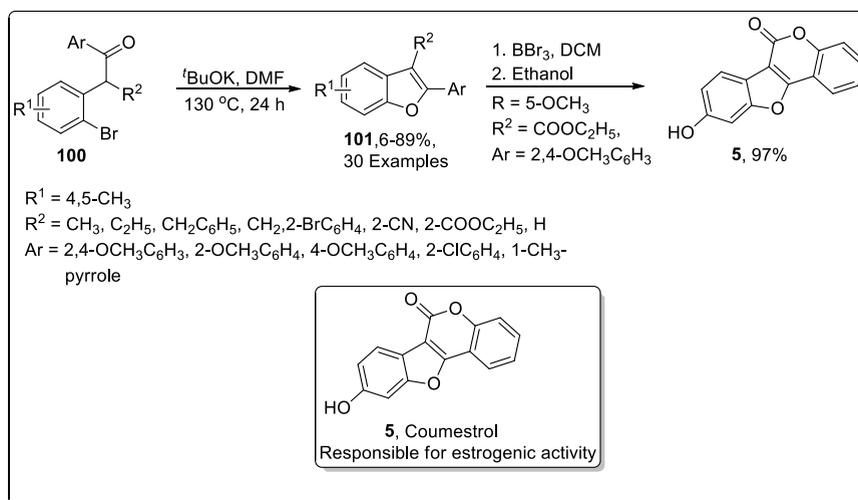
Scheme 31. Synthesis of Benzofuran Derivatives 103 by Using *tert*-Butoxide As a Catalyst
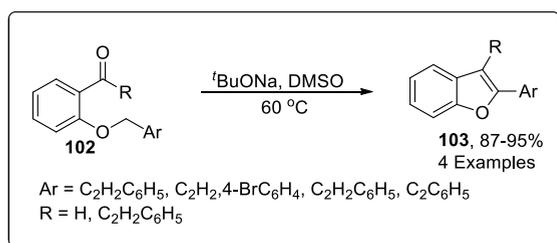
active compounds can be further utilized to develop efficient antitubercular agents (Scheme 10).

2.1.4. Benzofuran Synthesis via Nickel-Based Catalyst. In recent times, the catalytic role of nickel has been utilized by some research groups, thus expanding the transition metal induced synthesis of benzofuran heterocycles.[77] In 2021, Zhu[78] reported a novel and efficient synthetic methodology toward their synthesis. For this purpose, they utilized the nickel catalyst to provide activation energy for the nucleophilic addition reaction within the molecule, thereby furnishing benzofuran derivatives in noteworthy yields. The results indicated that the use of Ni(OTf)$_2$ as catalyst, 1,10-phenanthroline as ligand, and acetonitrile as solvent led to the high yields of benzofuran derivatives. The reaction pathway involved the combination of nickle salts with the ligand (1,10-Phen), followed by reduction via zinc powder and oxidative addition to generate nickle intermediate **A**. The generated intermediate **A** further under-

went nucleophilic addition, transmetalation, and finally subsequent removal of metal and water to furnish target molecules **41** in efficient yields (23−89%) (Scheme 11).

2.1.5. Benzofuran Synthesis via Rhodium-Based Catalyst. Among transition-metal-catalyzed organic syntheses, rhodium-based catalysts have acquired considerable weightage.[81] Recently, the rhodium-catalyzed multicomponent synthesis of optically active organic compounds has been achieved by Glorius et al.[79] In 2022, Kitano et al.[80] brought out the synthesis of (C4) substituted benzofurans by rhodium-mediated transfer of vinylene between vinyl carbonate **42** and meta-salicylic acid derivative **43**. They treated substituted benzamides **43** with vinylene carbonate **42** in the presence of cyclopentadienyl-based rhodium complex CpRh (as ligand) in a catalytic amount by using tetrachloroethane as a solvent to obtain widely substituted benzofuran heterocycles **44** in low to good yields (30−80%) (Scheme 12). The synthetic pathway was accomplished with four main steps, i.e., C−H activation, migratory insertion, nucleophilic substitution, and β-oxygen elimination, to achieve desired benzofuran derivatives **44** (Figure 11).

In 2022, Zhu et al.[82] carried out the arylation and subsequent cyclization between propargyl alcohols **46** and substituted aryl boronic acids **45** via relay rhodium-mediated catalysis to attain chemodivergent generation of benzofuran skeletons. Their synthetic route was processed by involving toluene sulfonic acid and tetrahydrofuran/water within the reaction medium. Substrates with electron-donating substituents have been observed to provide high yields of target molecules **47**. The synthetic route involved the β-specified carborhodation,

Scheme 32. Synthesis of Benzofuran Derivatives 105 by Using DBU As a Catalyst

R^1 = C$_6$H$_5$, 4-C$_2$H$_5$C$_6$H$_4$, 4-C$_4$H$_9$C$_6$H$_4$, 2,4-CH$_3$C$_6$H$_4$, 4-OCF$_3$C$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 3-CNC$_6$H$_4$
  thiophenyl
R^2 = C$_6$H$_5$, 4-OCH$_3$C$_6$H$_4$, 2-C$_4$H$_3$S, NTs-C$_7$H$_6$N
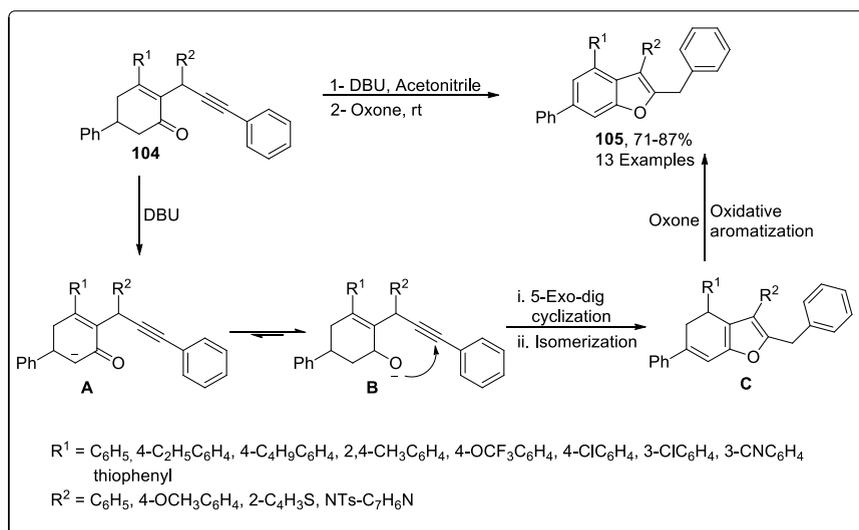
Scheme 33. Catalyst-Free Synthesis of Benzofuran Derivatives 108

R = C$_6$H$_5$, 4-OCH$_3$C$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, 4-C$_4$H$_9$C$_6$H$_4$, 4-FC$_6$H$_4$,
  4-ClC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 2-CH$_3$C$_6$H$_4$, 3-CH$_3$C$_6$H$_4$, 4OCH$_3$
  C$_6$H$_4$, 4-C$_4$H$_3$S, 4-C$_6$H$_5$C$_6$H$_4$, 4-C$_3$H$_5$C$_6$H$_4$, C$_4$H$_9$, CH$_3$
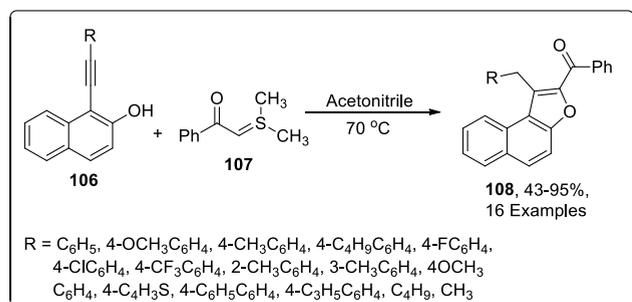
followed by hydrolysis and Bronsted-acid-mediated cyclization to furnish target molecules **47** (Scheme 13).

Facile and direct formation of C−H and C−X bonds is highly attributed to transition-metal-mediated and directing-group-accompanied bond formation.[82] There is very limited reported work concerning the C−H alkenylation or (DG migration) with 1,3-diynes due to arduous attainment of stereo- and regioselectivity. In 2023, Gong et al.[83] reported the rhodium-catalyzed novel synthesis of a benzofuran ring by C−H directing group migration between 1,3-diynes **49** and N-benzoxyaceta-mide **48**. It was inferred that rhodium-catalyzed annulation in the presence of NaOPiv·H$_2$O (additive) and dichloromethane (solvent) gave higher yields of target molecules **50**. The benzofuran derivatives **50** were achieved by undergoing C−H activation, migratory insertion, protonation, and intramolecular substitution (Scheme 14).

2.1.6. Benzofuran Synthesis via Gold- and Silver-Based Catalysts. In 2022, Li et al.[84] described a novel approach toward the formation of a benzofuran nucleus by treating alkynyl esters **51** and quinols **52** via gold-promoted catalysis. The use of a JohnPhosAuCl/AgNTf$_2$ catalyst and Ph$_2$SiF$_2$ additive in the presence of dichloroethane gave moderate to good yields. Then, the scope of various electron-donating and -withdrawing group substituted substrates was assessed by applying high yielding reaction conditions (Scheme 15). Their proposed mechanism was initiated by the formation of intermediate **A** as a result of a combination of a gold catalyst with alkynyl esters **51**. The intermediate **A** then underwent nucleophilic attack by quinols **52** to generate intermediate **B**, which was further subjected to sigmatropic rearrangement (Claisen), aromatization, and condensation to yield benzofuran heterocycles **53** (Figure 12).

The benzofuran-based heterocycle **53a** (obtained by applying standard reaction conditions) was further subjected to reduction followed by hydrolysis to attain compound **54**. The acid **54** was later transformed to benzofuran derivatives **55** which exhibit high potency against various microbes. Thus, gold-promoted
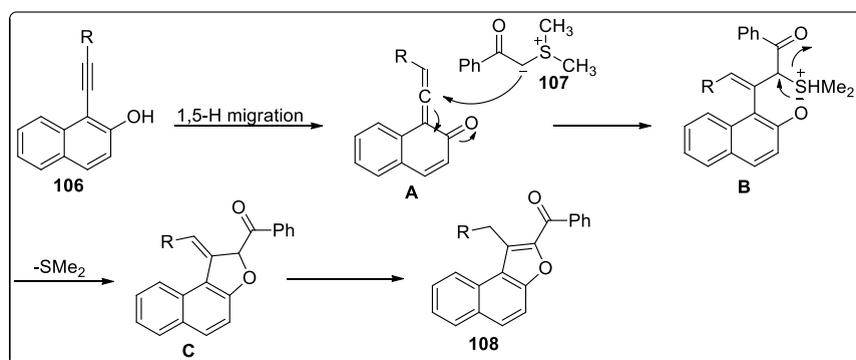
Figure 15. Proposed mechanism for the catalyst-free synthesis of benzofuran derivatives **108**.

Scheme 34. Catalyst-Free Synthesis of Benzofuran Heterocycles 110

110, 33-84%
19 Examples
R^1 = H, 5-Br, 5-F, 4-N(CH$_3$)$_2$, 5-Cl, 3-OCH$_3$
R^2 = H, 4-NO$_2$, 3-NO$_2$, 4-Cl, fused C$_4$H$_4$
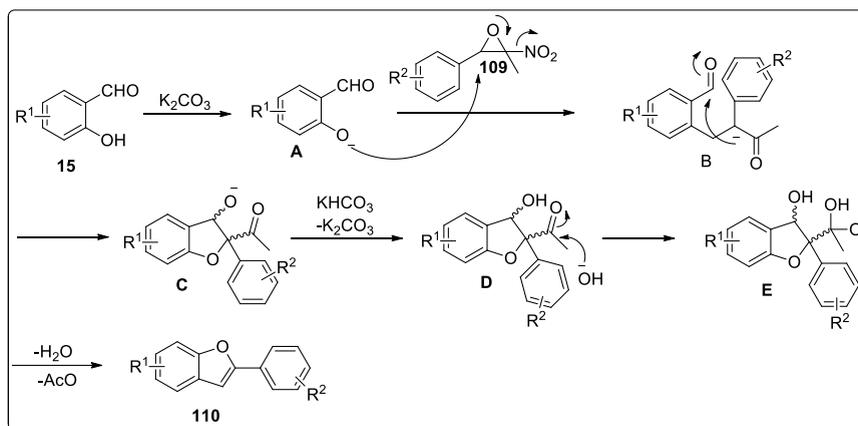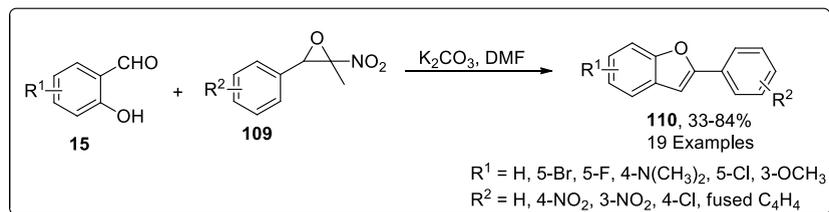
Figure 16. Proposed mechanism for the catalyst-free synthesis of benzofuran derivatives **110**.

Scheme 35. Catalyst-Free Synthesis of Benzofuran Derivatives 115

R = 4-OCH$_3$C$_6$H$_4$, 3,4-OCH$_3$C$_6$H$_3$, C$_6$H$_5$, 3,4,5-OCH$_3$C$_6$H$_2$, 4-N(C$_2$H$_5$)$_2$
Ar = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, 4-OCH$_3$C$_6$H$_4$, 3-OCH$_3$C$_6$H$_4$
    4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CNC$_6$H$_4$, 4-C$_6$H$_5$C$_6$H$_4$

115, 89-98%
27 Examples
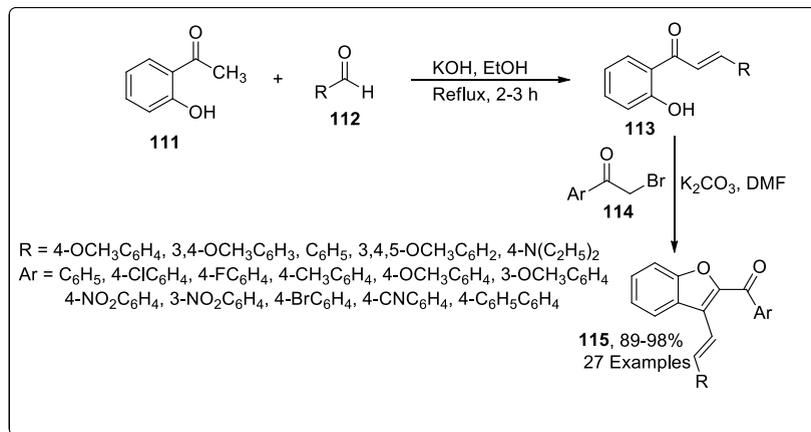
Scheme 36. Electrochemical Induced Synthesis of Benzofuran Heterocycles 118

118, 31-95%
18 Examples

R = C$_6$H$_5$, 4-CH$_3$C$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 2-CH$_3$C$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 4-ClC$_6$H$_4$,
    4-OCH$_3$C$_6$H$_4$, C$_4$H$_9$, 4-C$_4$H$_3$S
R' = H, 4-Br, 4-CH$_3$
Ar = C$_6$H$_5$, 4-ClC$_6$H$_4$, 4-CH$_3$C$_6$H$_4$, C$_6$H$_{11}$, thiophenyl
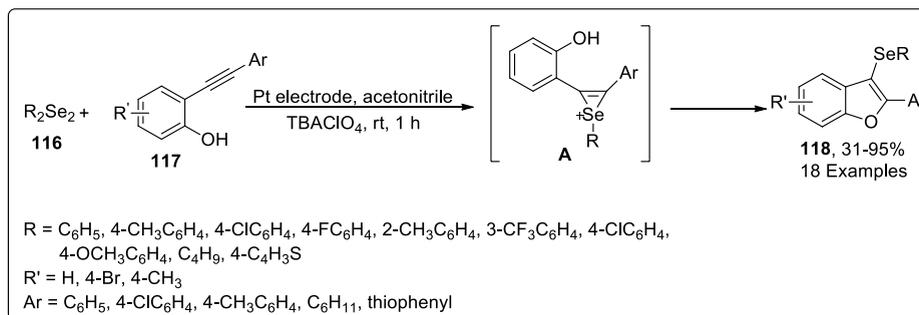
cyclization between alkynyl esters and quinols paved the pathway toward the generation of medicinally active benzofuran derivatives **55** (Scheme 16).

Taking into account the unparalleled contribution of benzofuran-substituted heterocycles in pharmaceutical chemistry, Hu et al.[85] in 2022 utilized silver-based catalyst, i.e.,

Scheme 37. Synthesis of Benzofuran Nucleus 121 by Employing an Interrupted Pummerer Reaction

R^1 = C$_2$H$_4$C$_6$H$_5$, C$_2$H$_4$OCO-4-CH$_3$C$_6$H$_4$, 4-CH$_3$C$_6$H$_4$
    4-ClC$_6$H$_4$. 4-C$_4$H$_9$
R^2 = C$_2$H$_5$, 4-CH$_3$C$_6$H$_4$, 4-BrC$_6$H$_4$

Scheme 38. Synthesis of Benzofuran Nucleus 123 by Employing Wittig Reaction

R^1 = H, 4-CH$_3$, 4-OCH$_3$, 4-Br, 4-Cl, 5-OCH$_3$, 6-OCH$_3$
R^2 = C$_6$H$_5$, 4-OCH$_3$C$_6$H$_4$, 4-BrC$_6$H$_4$, 3-BrC$_6$H$_4$. 2-BrC$_6$H$_4$
    C$_4$H$_3$O, CH$_3$, H, C$_2$H$_2$
R^3 = C$_3$H$_7$, 4-CH$_3$C$_6$H$_4$, 4-OCH$_3$C$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$,
    3-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, C$_6$H$_5$, furanyl, thiophenyl, naphthyl
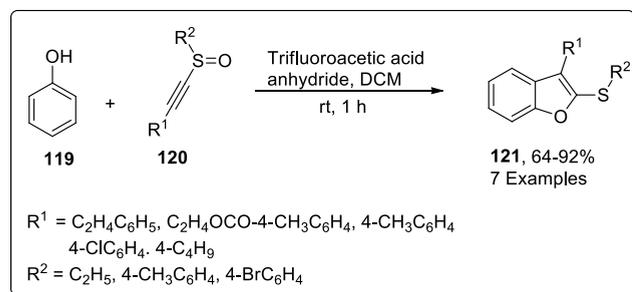
AgNTf$_2$, for Friedel–Crafts propargylation, Michael addition, and hydride shift between phenol **56** and CF$_3$-substituted propynols **57** to yield benzofuran derivatives **58** in excellent yields. Similarly, Hashmi's group[86] employed a bimetallic catalytic system, i.e., gold–silver (Ph$_3$PAuCl/AgNTf$_2$/Phen), to contribute toward the synthesis of heterocyclic organic compounds. They utilized the oxidation–reduction characteristics of gold with its ability to activate the carbophilic (π) acidity. They reported the synthesis of benzofuran heterocycles **60** by treating readily accessible substituted phenols **56** with alkynylbenziodoxoles **59** over a Au–Ag bimetallic catalyst. The reaction proceeded via alkynylation and oxyalkynylation to give alkyne-substituted benzofurans **60** regioselectively (Scheme 17).

2.1.7. Benzofuran Synthesis via Ruthenium-Based Catalyst. In 2021, Zheng and co-workers[87] reported the synthesis of benzofuran derivatives **64** by ruthenium-catalyzed reaction between alkynes **62** and *m*-hydroxybenzoic acids **61**. The reaction proceeded via C–H alkenylation of *m*-hydroxybenzoic acids followed by oxygen-induced annulation by employing magnesium acetate as a base and γ-valerolactone (GVL) as a solvent to carry out facile aerobic oxidation. It was interpreted that benzoic acids substituted with electron-withdrawing groups, i.e., Cl, Br, CF$_3$, and OH, resulted in lower yields of target molecules as compared to those with electron-donating groups, i.e., CH$_3$ and OCH$_3$ (−ve inductive and +ve resonance effect) (Scheme 18).

Substituted alkyne **65** and methoxy-substituted hydroxybenzoic acid **66** were treated under standard conditions to synthesize benzofuran derivatives **67** and **67′**. These derivatives were subjected to reaction in the presence of trifluoroacetic acid followed by demethylation via BBr$_3$ to achieve a naturally
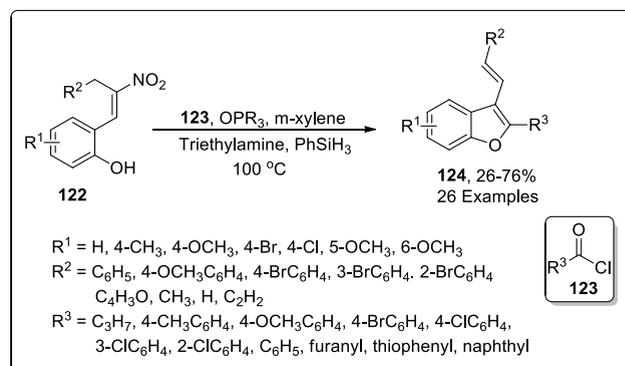
occurring biologically active benzofuran-constituting organic compound, i.e., diptoindonesin G **68**[88] (Scheme 19).

Similarly, Kotha et al.[89] treated substituted phenols **56** with allyl bromide in the presence of acetone and potassium carbonate to obtain diallyl compound **69**. The diallyl compound **69** was further reacted in the presence of a ruthenium-based catalyst and toluene, followed by subsequent treatment using a Grubbs II generation catalyst to obtain benzofuran derivatives **70** (Scheme 20).

The benzannulation strategy was further extended to achieve the total synthesis of biologically potent phenylpropanoids. Compound **71** was subjected to olefin migration by using potassium *tert*-butoxide followed by DDQ-mediated oxidation to obtain the aldehyde derivative in 77% yield. The aldehyde moiety was then subjected to ring conversion metathesis under standard conditions to obtain 7-methoxywutaifuranal **72**. The naturally occurring 7-methoxywutaifuranal **72** afforded 7-methoxywutaifuranol **73** in 96% yield upon reduction. On the other side, an esterification reaction was carried out to convert 7-methoxywutaifuranal **72** to 7-methoxywutaifuranate **74** in 90% yield. These naturally occurring phenylpropanoids act as anticancer and antidiabetic agents. Moreover, they have also been found to be effective against inflammatory, bacterial, and heart diseases[90] (Scheme 21).

2.2. Benzofuran Synthesis via Lewis-Acid-Based Catalysis. Lewis acids are among the most widely used catalysts that usually decrease the activation energy by harmonizing the reactant's lone pair with the lowest unoccupied orbital (LUMO). The potential of Lewis acids to assimilate the
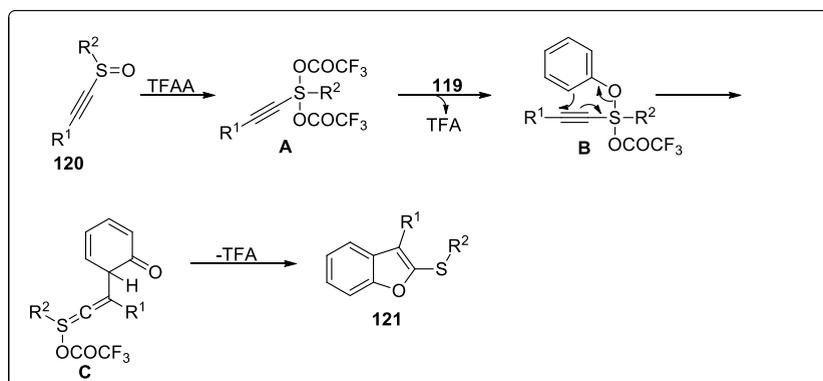
Figure 17. Proposed mechanism for the synthesis of benzofuran heterocycles **121** by employing an interrupted Pummerer reaction.
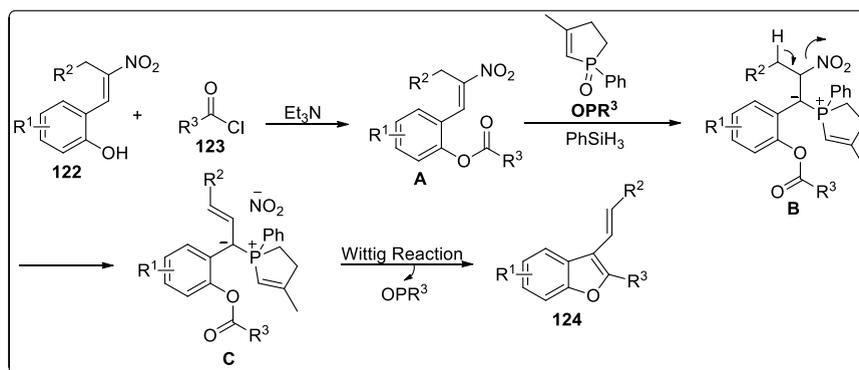
Figure 18. Proposed mechanism for the synthesis of benzofuran nucleus **124** by employing the Wittig reaction.

Scheme 39. PIDA-Mediated Synthesis of Benzofuran Nucleus 125
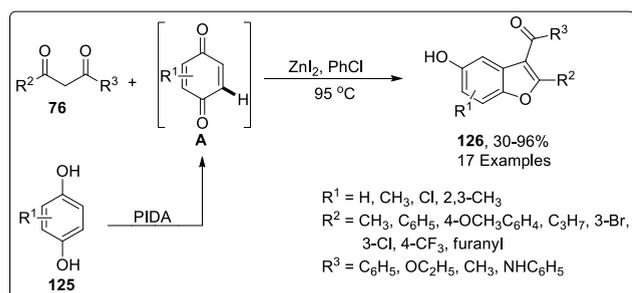
Scheme 40. Synthesis of Benzofuran Nucleus 128 and 129 by Using *C*-Glycosyltransferase-Based Coumarins
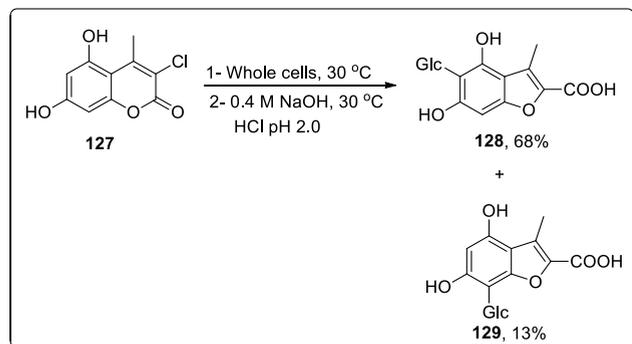
Scheme 41. Synthesis of 2,3-Disubstituted Benzofurans 131 by Using Triflimide As a Catalyst
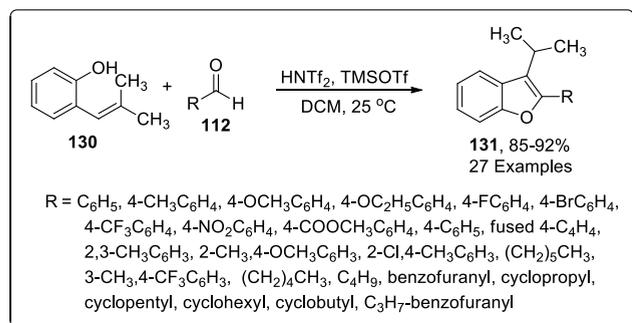
electron pairs actually governs the productivity of the reaction.[91] In 2021, Reddy et al.[92] executed Lewis-acid-catalyzed reaction

(Domino reaction) toward the synthesis of benzofuran derivatives. They employed a boron trifluoride diethyl etherate promoted Domino reaction between 2,4-diyn-1-ols **75** and dicarbonyl compounds **76** in the presence of base. This novel synthetic route proceeded through Lewis-acid-promoted propargylation, followed by potassium carbonate-mediated intramolecular cyclization, isomerization, and finally benzannulation to procure benzofuran derivatives **77** in efficient yields (75−91%). The synthetic strategy was also applied to generate the three naturally occurring eustifoline D analogues **77**(**g−i**), obtained by treating **75g** as a precursor, which are of great pharmaceutical significance owing to the presence of a biologically active carbazole scaffold[93] (Scheme 22).

In 2021, Liu et al.[94] reported the iron-chloride-catalyzed ring-closing reaction between trifluoromethylselenolating reagent **78** and substituted alkynyl benzenes **79** utilizing toluene as solvent to furnish substituted benzofuran derivatives **80**. The reaction was proposed to be accomplished via Lewis-acid-promoted intramolecular cyclization (Scheme 23).

Similarly, recently in this year, the Yang group[95] also reported a novel and facile Lewis acid (scandium triflate) promoted synthetic route toward the construction of benzofuran scaffolds. They demonstrated scandium triflate-mediated [4 + 1] cycloaddition of isocyanide and *o*-quinone methides (prepared within the reaction from *o*-hydroxybenzhydryl alcohol **81**) employing toluene as solvent to acquire substituted amino-benzofurans **82** in eco-friendly conditions. Similarly, the synthesis of amino-substituted benzofurans **84** was reported by Lin et al.[96] in 2022, via scandium-triflate-catalyzed [4 + 1] cycloaddition between isocyanide **83** and *ortho*-quinone methides. This novel synthetic methodology is highly efficient and high yielding with moderate reaction conditions involving nucleophilic addition, cyclization, and isomerization (Scheme 24).

2.3. Benzofuran Synthesis via Bronsted-Acid-Mediated Catalysis. For the construction of carbon−carbon bonds, Bronsted-acid-mediated reactions have gained substantial significance in organic synthesis.[97] Taking into account the efficiency of Bronsted-acid-catalyzed reactions, Chen et al.[98] in 2022 proposed the triflic-acid-mediated reaction of substituted quinone imine ketals (QIK) **86** with substituted dicarbonyl compounds **85** involving water and HFIP (hexafluoroisopropanaol) medium to achieve substituted benzofuran cores **87** in high yields (Scheme 25).

Another example of triflic-acid-mediated synthesis of benzofuran derivatives was presented by Mandal and Balamurugan[99] by using *o*-alkynylphenols. This novel synthetic approach
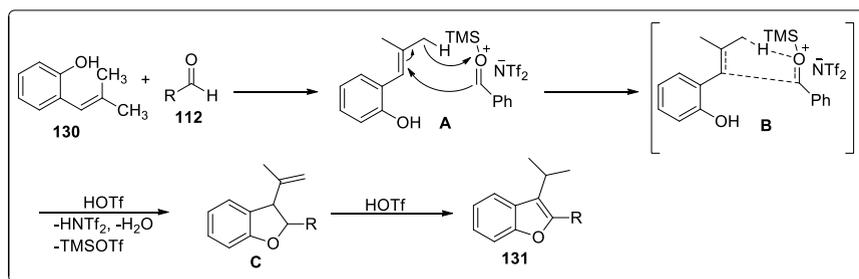
Figure 19. Proposed mechanism for the synthesis of benzofuran derivatives **131** by using triflimide as a catalyst.

proceeded by the protonation of vinylogous esters **88** (obtained via o-alkynyl phenols) by TfOH to obtain oxocarbenium ion **A**, which was then followed by the addition of alkyne to release vinyl triflate **B**. This vinyl triflate **B** was then subjected to the oxa-Michael reaction, finally leading to the synthesis of substituted benzofuran derivatives **89**. HFIP was selected as solvent for the developed synthetic route owing to its ability to stabilize the charged intermediates (Scheme 26 and Figure 13).

In 2021, Pirouz et al.[100] proposed the heterocyclic ring formation by treating benzoquinones **91** and compound **90** via a one-pot synthetic protocol. This novel methodology proceeded via an acetic acid catalyst, employing toluene as solvent to yield benzofuran derivatives. Acetic acid protonated the benzoquinone to generate intermediate **A**, which resulted in the synthesis of benzofuran derivative **92** by undergoing ring opening, addition of water, oxidation, and lactonization (Scheme 27).

2.4. Benzofuran Synthesis via Visible-Light-Mediated Catalysis. Considering the wide utilization of visible-light-promoted organic reactions,[101] in 2022, Li et al.[102] carried out the novel synthetic route to synthesize benzofuran heterocycles **94** between disulfides and enynes **93** to afford high yields of benzofuran heterocycles. Their synthetic route began with the generation of an enyene peroxo radical, followed by the formation of peroxoenynthio intermediate **A**, which further underwent a 1,5-proton transfer reaction in N-methyl pyrrolidone (NMP) solvent to yield benzofuran derivatives **94** by the removal of the hydroxyl group. The reaction pathway was also utilized to carry out the gram-scale synthesis of target molecules. In the same year, Liu et al.[103] also employed visible-light-mediated cyclization to achieve carbonyl and hydroxyl group substituted benzofuran heterocycles **96**. They treated 1,6-enynes **93** and bromomalonates **95** via visible-light-promoted cyclization without employing any photocatalyst, oxidant, transition metal, and additive, thereby reporting an atom-economic synthetic protocol. This reaction route involved the radical-mediated pathway involving 5-exo-dig cyclization, nucleophilic substitution, and aromatization to afford target molecules **96** (Scheme 28).

2.5. Base-Catalyzed Benzofuran Synthesis. Among the recently employed synthetic pathways toward the synthesis of benzofuran derivatives, various bases have been utilized as catalysts for the construction of these heterocyclic scaffolds. In 2022, Koca et al.[104] reported the use of triethylamine as a basic catalyst in the Rap–Stoermer reaction to obtain benzofuran derivatives **99** (Scheme 29). In their synthetic methodology, α-haloketones **98** were treated with diversely substituted salicylaldehydes **97** via triethylamine-catalyzed Dieckmann-like aldol condensation in neat conditions that resulted in remarkable yields (81–97%) of benzofuran derivatives **99** (Figure 14).

In the same year, the Zhang group[105] devised another novel base-mediated synthesis of benzofuran heterocyclic cores. They carried out the transition-metal-free, potassium tert-butoxide-catalyzed synthesis of benzofuran derivatives **101** by treating substituted o-bromobenzylvinyl ketones **100** through intramolecular cyclization, using dimethylformamide as solvent. This novel synthetic approach encompasses a broad range of substituents and has also been applied toward the synthesis of a medicinally significant natural product, i.e., coumestrol **5** (Scheme 30).

In 2023, tert-butoxide was employed as a catalyst toward the synthesis of benzofuran heterocycles **103** in the presence of dimethyl sulfoxide solvent by Wang's group[106] (Scheme 31).

The Reddy group[107] proposed a novel methodology by employing nonaromatic precursors to obtain benzofuran derivatives **105**. They employed DBU (1,8-diazabicyclo(5.4.0)-undec-7-ene) promoted cyclization (5-exo-dig cyclization) of 2-propargyl cyclohexenone **104** followed by oxidation-induced formation of a benzene ring utilizing oxone as an oxidant. The direct approach toward the procurement of target molecules and mild and atom-economic reaction conditions are some of the essential features of this developed protocol (Scheme 32).

2.6. Catalyst-Free Benzofurans Synthesis. Catalyst-free synthesis has gained a valuable place in novel methodologies regarding the synthesis of benzofuran derivatives. Yu et al.[108] reported the catalyst-free synthesis of benzofuran heterocycles **108** by successive reactions of hydroxyl-substituted aryl alkynes **106** and sulfur ylides **107** which included the formation of isomers followed by the addition of nucleophile to generate intermediate **B**. The subsequent cyclization of intermediate **B** then led to the formation of an aromatic ring. The successive reactions between the substrates were carried out in acetonitrile in the absence of any catalyst to afford tricyclic benzofuran derivatives **108** via a facile manner (Scheme 33 and Figure 15).

To further investigate the catalyst-free synthetic pathways, Ranjbari and Tavakol[109] treated substituted salicylaldehydes **15** with diversely substituted nitro epoxides **109** in the absence of catalyst using potassium carbonate and dimethylformamide. As a result, substituted benzofuran derivatives **110** were obtained in efficient yields (33–84%) (Scheme 34). The reaction mechanism was proposed to move forward by deprotonation, followed by epoxide ring opening to generate intermediate **B**. The intermediate **B** further underwent intramolecular cyclization followed by the elimination of water to yield benzofuran derivatives **110** (Figure 16).

Another catalyst-free, one-pot approach toward the synthesis of benzofuran derivatives was described by Mundhe et al.[110] recently. They carried out the condensation reaction between aryl ketones **111** and substituted benzaldehydes **112** to attain α,β-unsaturated ketones **113**. These ketones were treated with

phenacyl bromides **114** via potassium-carbonate-mediated alkylation followed by subsequent condensation to furnish required benzofuran derivatives **115** in a facile manner (Scheme 35).

2.7. Benzofuran Synthesis by Employing Miscellaneous Synthetic Strategies. *2.7.1. Benzofuran Synthesis via an Electrochemical Approach.* The Doerner group[111] reported the synthesis of benzofuran derivatives by employing electrochemical conditions. They carried out the cyclization of 2-alkynylphenols **117** and various diselenides **116** in the presence of platinum electrodes using acetonitrile as the solvent, thereby providing substituted benzofuran heterocycles **118** in high yields. The synthetic pathway involved the formation of seleniranium intermediate **A**, which further underwent nucleophilic cyclization to furnish benzofuran derivatives **118** (Scheme 36).

2.7.2. Benzofuran Synthesis via Interrupted Pummerer Reaction. In 2022, Kobayashi et al.[112] envisioned the synthesis of benzofuran derivatives by treating phenol **119** and alkynyl sulfoxide **120** via interrupted Pummerer reaction. Numerous derivatives of benzofuran heterocycles **121** have been prepared by this novel methodology considering the facile accessibility of alkynyl sulfoxides (Scheme 37). The synthetic pathway was proposed to be accomplished by involving electrophilic activation of alkynyl sulfoxides **120** with trifluoroacetic acid anhydride proceeded by nucleophilic substitution with phenol **119** to generate intermediate **B** via an interrupted Pummerer reaction. The intermediate **B** then underwent sigmatropic rearrangement and deprotonation to yield target molecules **121** (Figure 17).

2.7.3. Benzofuran Synthesis by Employing Wittig Reaction. Liou et al.[113] demonstrated the synthesis of alkenyl-substituted benzofuran derivatives **124** by phosphine-catalyzed Wittig reaction. At first, *o*-acylated nitrostyrenes **A** were obtained by treating nitrostyrenes **122** with substituted acyl chlorides **123** using triethylamine. *o*-Acylated nitrostyrenes **A** were then subjected to reaction with phosphine [which was obtained within the reaction mixture from the reduction of phosphine oxide (OPR$_3$) and PhSiH$_3$] via Phospha−Michael addition. The resulting phosphonium ylide **C** on release of nitrous acid underwent Wittig reaction to result in benzofuran derivatives **124** in a one-pot synthesis (Scheme 38 and Figure 18).

2.7.4. Benzofuran Synthesis by Employing PIDA As an Oxidant. In 2022, Lin et al.[114] proposed the synthesis of benzofuran derivatives by utilizing PIDA (phenyliodonium diacetate) as an oxidant in oxidative coupling reaction of hydroquinone **125** and dicarbonyl compounds **76** followed by cyclization. The reaction was carried out in the presence of zinc iodide and phenyl chloride, thereby leading to the efficient synthesis of target molecules **126** (Scheme 39).

2.7.5. Benzofuran Synthesis by Using C-Glycosyltransferase-Based Coumarins As Precursors. Besides the discovery of plant-based *C*-glycosyltransferase, recently coumarin-based *C*-glycosyltransferases have also been found. These coumarin *C*-glycosyltransferases **127** have been employed for the synthesis of benzofuran derivatives by Chen et al. in 2021.[115] First, they carried out the total synthesis of coumarin *C*-glycosyltransferase by adding D-glucose and utilizing MACGT as a (whole cell) biocatalyst. Then, the synthesized coumarin *C*-glycosidase was cyclized in the presence of sodium hydroxide followed by subsequent acidification to achieve two novel carboxylic acid substituted benzofuran derivatives **128** and **129** (Scheme 40).

2.7.6. Benzofuran Synthesis by Employing HNTf$_2$/TMSOTf. A triflimide/trimethylsilyl trifluoromethanesulfonate-catalyzed, transition-metal-free synthesis of benzofuran heterocycles **131** has been recently proposed by the Tan group.[116] They reported the synthesis of a series of substituted benzofuran derivatives **131** by treating substituted aldehydes **112** with substituted *o*-alkenyl phenols **130** by employing triflimide as a catalyst and trimethylsilyl trifluoromethanesulfonate as an additive in dichloromethane (Scheme 41). The reaction mechanism was proposed to move forward by the TMSNTf$_2$-mediated (obtained by HNTf$_2$ and TMSOTf) generation of intermediate **B**. The intermediate **B** was further subjected to a triflic-acid-mediated nucleophilic substitution reaction, followed by the removal of TfOH to furnish benzofuran derivatives **131** (Figure 19).

3. CONCLUSION

This review provides a detailed outlook of all novel and facile synthetic routes to yield benzofuran heterocycles, reported in 2021−2023. Most of the reported methodologies mainly involved the synthesis of benzofuran heterocycles by employing various types of cyclization processes (intramolecular, radical induced, benzannulation, etc.) under various reaction conditions, i.e., Lewis/Bronsted acids, bases, photochemical, as well as catalyst-free conditions. Some protocols also involved cycloaddition reactions, condensation reactions, coupling reactions involving nucleophilic addition, or nucleophilic substitution processes to yield the target molecules. For this purpose, various transition metals, i.e., copper, palladium, nickel, gold, silver, rhodium, ruthenium, etc., have been employed to avail their catalytic usage, thereby furnishing the benzofuran nucleus in high yields. Almost all the recently developed protocols entailed the high yielding and broad substrate scope featuring reaction conditions by utilizing facile precursors; however, a few of the developed strategies could be further extended to explore their beneficiary aspects toward the synthesis of natural products and biologically active organic compounds. Moreover, considering the undeniable toxic effects of environmental pollution, eco-friendly methods have also been devised to achieve benzofuran derivatives in high yields via catalyst-free synthesis. However, these developments are few in number, and their applicability toward the accomplishment of medicinally active organic compounds and natural products has not been explored yet. These findings interpret that there is still room for research to advance the established protocols further to investigate their profitable aspects in medicinal and synthetic organic chemistry.

■ ASSOCIATED CONTENT

Data Availability Statement

All the data for this study are contained in the manuscript.

■ AUTHOR INFORMATION

Corresponding Authors

Ameer Fawad Zahoor − *Department of Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan;* orcid.org/0000-0003-2127-8848; Email: fawad.zahoor@gcuf.edu.pk

Ali Irfan − *Department of Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan;* orcid.org/0000-0002-8977-3303; Email: raialiirfan@gmail.com

Magdi E. A. Zaki − *Department of Chemistry, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11623, Saudi Arabia*; Email: mezaki@imamu.edu.sa

Authors

Aqsa Mushtaq − *Department of Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan*

Sajjad Ahmad − *Department of Chemistry, University of Engineering and Technology Lahore, 38000 Faisalabad, Pakistan*

Muhammad Jawwad Saif − *Department of Applied Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan*; ⓘ orcid.org/0000-0002-9589-876X

Atta ul Haq − *Department of Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan*; ⓘ orcid.org/0000-0003-2975-6381

Samreen Gul Khan − *Department of Chemistry, Government College University Faisalabad, 38000 Faisalabad, Pakistan*

Aamal A. Al-Mutairi − *Department of Chemistry, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11623, Saudi Arabia*

Sami A. Al-Hussain − *Department of Chemistry, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11623, Saudi Arabia*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.4c02677

Author Contributions

A.M.: Literature review (formal analysis), writing—original draft preparation. **A.F.Z.**: Conceptualization, resources, writing—review and editing, supervision, project administration. **S.A.**: Visualization; writing—review and editing, literature survey (formal analysis). **M.J.S.**: Literature survey (formal analysis), writing—review and editing. **A.H.**: writing—review and editing, sofware. **S.G.K.**: software, writing—review and editing. **A.A.Al-M.**: writing—review and editing, formal analysis, resources. **A.I.**: Conceptualization, writing—review and editing, visualization, funding acquisition. **S.A.Al-H.**: Resources, data curation, writing—review and editing, funding acquisition. **M.E.A.Z.**: Visualization, project administration, writing—review and editing, and funding acquisition.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Chand, K.; Rajeshwari; Hiremathad, A.; Singh, M.; Santos, M. A.; Keri, R. S. A review on antioxidant potential of bioactive heterocycle benzofuran: Natural and synthetic derivatives. *Pharmacol. Rep.* **2017**, *69* (2), 281−295.

(2) Perkin, W. H. XXIX.—On some new bromine derivatives of coumarin. *J. Chem. Soc.* **1870**, *23*, 368−371.

(3) Khanam, H.; et al. Bioactive Benzofuran derivatives: A review. *Eur. J. Med.. Chem.* **2015**, *97*, 483−504.

(4) Hiremathad, A.; Patil, M. R.; Chethana, K. R.; Chand, K.; Santos, M. A.; Keri, R. S. Benzofuran: An emerging scaffold for antimicrobial agents. *RSC Adv.* **2015**, *5*, 96809−96828.

(5) Manna, K.; Agrawal, Y. K. Design, synthesis, and antitubercular evaluation of novel series of 3-benzofuran-5-aryl-1-pyrazolyl-pyridyl-methanone and 3-benzofuran-5-aryl-1-pyrazolylcarbonyl-4-oxo-naphthyridin analogs. *Eur. J. Med. Chem.* **2010**, *45* (9), 3831−3839.

(6) Faiz, S.; Zahoor, A. F.; Ajmal, M.; Kamal, S.; Ahmad, S.; Abdelgawad, A. M.; Elnaggar, M. E. Design, Synthesis, Antimicrobial Evaluation, and Laccase Catalysis Effect of Novel Benzofuran−Oxadiazole and Benzofuran−Triazole Hybrids. *J. Heterocycl. Chem.* **2019**, *56* (10), 2839−2852.

(7) Saeed, S.; Zahoor, A. F.; Kamal, S.; Raza, Z.; Bhat, M. A. Unfolding the Antibacterial Activity and Acetylcholinesterase Inhibition Potential of Benzofuran-Triazole Hybrids: Synthesis, Antibacterial, Acetylcholinesterase Inhibition, and Molecular Docking Studies. *Molecules* **2023**, *28* (16), 6007.

(8) Irfan, A.; Faisal, S.; Zahoor, A. F.; Noreen, R.; Al-Hussain, S. A.; Tuzun, B.; Javaid, R.; Elhenawy, A. A.; Zaki, M. E. A.; Ahmad, S.; Abdellattif, M. H. In Silico Development of Novel Benzofuran-1,3,4-Oxadiazoles as Lead Inhibitors of M. tuberculosis Polyketide Synthase 13. *Pharmaceuticals* **2023**, *16* (6), 829.

(9) Xu, Z.; Xu, D.; Zhou, W.; Zhang, X. Therapeutic potential of naturally occurring benzofuran derivatives and hybrids of benzofurans with other pharmacophores as antibacterial agents. *Curr. Top. Med. Chem.* **2022**, *22* (1), 64−82.

(10) Irfan, A.; Faisal, S.; Ahmad, S.; Saif, M. J.; Zahoor, A. F.; Khan, S. G.; Javid, J.; Al-Hussain, S. A.; Muhammed, M. T.; Zaki, M. E. A. An Exploration of the Inhibitory Mechanism of Rationally Screened Benzofuran-1,3,4-Oxadiazoles and-1,2,4-Triazoles as Inhibitors of NS5B RdRp Hepatitis C Virus through Pharmacoinformatic Approaches. *Biomedicines* **2023**, *11* (11), 3085.

(11) Rida, S. M.; El-Hawash, S. A.; Fahmy, H. T.; Hazza, A. A.; El-Meligy, M. M. Synthesis and in vitro evaluation of some novel benzofuran derivatives as potential anti-HIV-1, anticancer, and antimicrobial agents. *Arch. Pharm. Res.* **2006**, *29*, 16−25.

(12) Chen, Y.; Chen, R.; Yuan, R.; Huo, L.; Gao, H.; Zhuo, Y.; Chen, X.; Zhang, C.; Yang, S. Discovery of New Heterocyclic/Benzofuran Hybrids as Potential Anti-Inflammatory Agents: Design, Synthesis, and Evaluation of the Inhibitory Activity of Their Related Inflammatory Factors Based on NF-κB and MAPK Signaling Pathways. *Int. J. Mol. Sci.* **2023**, *24* (4), 3575.

(13) Pagotti, M. C.; Dias, H. J.; Candido, A. C. B.; Oliveira, T. A.; Borges, A.; Oliveira, N. D.; Lopes, C. D.; Orenha, R. P.; Parreira, R. L. T.; Crotti, A. E. M.; Magalhães, L. G. Exploring Synthetic Dihydrobenzofuran and Benzofuran Neolignans as Antiprotozoal Agents against Trypanosoma cruzi. *Pharmaceutics* **2023**, *15* (3), 754.

(14) Reddy, K. A.; Lohray, B. B.; Bhushan, V.; Bajji, A. C.; Reddy, K. V.; Reddy, P. R.; Krishna, T. H.; Rao, I. N.; Jajoo, H. K.; Rao, N. V. S. M.; Chakrabarti, R.; Dileepkumar, T.; Rajagopalan, R. Novel Antidiabetic and Hypolipidemic Agents. 3. Benzofuran-Containing Thiazolidinediones. *J. Med. Chem.* **1999**, *42* (11), 1927−1940.

(15) Bhukya, B.; Shukla, A.; Chaturvedi, V.; Trivedi, P.; Kumar, S.; Khan, F.; Negi, A. S.; Srivastava, S. K. Design, synthesis, in vitro and in silico studies of 2, 3-diaryl benzofuran derivatives as antitubercular agents. *Bioorg. Chem.* **2020**, *99*, No. 103784.

(16) Dawood, K. M.; Abdel-Gawad, H.; Rageb, E. A.; Ellithey, M.; Mohamed, H. A. Synthesis, anticonvulsant, and anti-inflammatory evaluation of some new benzotriazole and benzofuran-based heterocycles. *Bioorg. Med. Chem.* **2006**, *14* (11), 3672−3680.

(17) Ono, M.; Kung, M. P.; Hou, C.; Kung, H. F. Benzofuran derivatives as Aβ-aggregate-specific imaging agents for Alzheimer's disease. *Nucl. Med. Biol.* **2002**, *29* (6), 633−642.

(18) Abdelhafez, O. M.; Amin, K. M.; Ali, H. I.; Abdalla, M. M.; Ahmed, E. Y. Design, synthesis and anticancer activity of benzofuran derivatives targeting VEGFR-2 tyrosine kinase. *RSC Adv.* **2014**, *4*, 11569−11579.

(19) Irfan, A.; Zahoor, A. F.; Rasul, A.; Al-Hussain, S. A.; Faisal, S.; Ahmad, S.; Noor, R.; Muhammed, M. T.; Zaki, M. E. A. BTEAC Catalyzed Ultrasonic-Assisted Synthesis of Bromobenzofuran-Oxadiazoles: Unravelling Anti-HepG-2 Cancer Therapeutic Potential through In Vitro and In Silico Studies. *Int. J. Mol. Sci.* **2023**, *24* (3), 3008.

(20) Irfan, A.; Faiz, S.; Rasul, A.; Zafar, R.; Zahoor, A. F.; Kotwica-Mojzych, K.; Mojzych, M. Exploring the Synergistic Anticancer

Potential of Benzofuran—Oxadiazoles and Triazoles: Improved Ultrasound- and Microwave-Assisted Synthesis, Molecular Docking, Hemolytic, Thrombolytic and Anticancer Evaluation of Furan-Based Molecules. *Molecules* **2022**, *27* (3), 1023.

(21) Negi, M.; Singh, S.; Kumar, G.; Afaque, N.; Negi, M. A review synthesis and evaluation of novel benzofuran derivatives as potent anticancer and anti-bacterial activity. *Bio Gecko* **2023**, *12* (3), 6477.

(22) Rádl, S.; Hezký, P.; Konvička, P.; Krejčí, I. Synthesis and analgesic activity of some substituted 1-benzofurans and 1-benzothiophenes. *Collect. Czechoslov. Chem. Comm.* **2000**, *65*, 1093−1108.

(23) Kenchappa, R.; Bodke, Y. D. Synthesis, analgesic and anti-inflammatory activity of benzofuran pyrazole heterocycles. *Chem. Data Collect.* **2020**, *28*, No. 100453.

(24) Graham, S. L.; Hoffman, J. M.; Gautheron, P.; Michelson, S. R.; Scholz, T. H.; Schwam, H.; Shepard, K. L.; Smith, A. M.; Smith, R. L. Topically active carbonic anhydrase inhibitors. 3. Benzofuran-and indole-2-sulfonamides. *J. Med. Chem.* **1990**, *33* (2), 749−754.

(25) Eldehna, W. M.; Nocentini, A.; Elsayed, Z. M.; Al-Warhi, T.; Aljaeed, N.; Alotaibi, O. J.; Al-Sanea, M. M.; Abdel-Aziz, H. A.; Supuran, C. T. Benzofuran-based carboxylic acids as carbonic anhydrase inhibitors and antiproliferative agents against breast cancer. *ACS Med. Chem. Lett.* **2020**, *11* (5), 1022−1027.

(26) Irfan, A.; Faisal, S.; Ahmad, S.; Al-Hussain, S. A.; Javed, S.; Zahoor, A. F.; Parveen, B.; Zaki, M. E. Structure-Based Virtual Screening of Furan-1, 3, 4-Oxadiazole Tethered N-phenylacetamide Derivatives as Novel Class of hTYR and hTYRP1 Inhibitors. *Pharmaceuticals* **2023**, *16*, 344.

(27) Suzuki, K.; Okawara, T.; Higashijima, T.; Yokomizo, K.; Mizushima, T.; Otsuka, M. Inhibitory activities against topoisomerase I and II by isoaurostatin derivatives and their structure−activity relationships. *Bioorg. Med. Chem. Lett.* **2005**, *15* (8), 2065−2068.

(28) Asoh, K.; Kohchi, M.; Hyoudoh, I.; Ohtsuka, T.; Masubuchi, M.; Kawasaki, K.; Ebiike, H.; Shiratori, Y.; Fukami, T. A.; Kondoh, O.; Tsukaguchi, T.; Ishii, N.; Aoki, Y.; Shimma, N.; Sakaitani, M. Synthesis and structure−activity relationships of novel benzofuran farnesyl-transferase inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19* (6), 1753−1757.

(29) Zhang, X.; Huang, H.; Zhang, Z.; Yan, J.; Wu, T.; Yin, W.; Sun, Y.; Wang, X.; Gu, Y.; Zhao, D.; Cheng, M. Design, synthesis and biological evaluation of novel benzofuran derivatives as potent LSD1 inhibitors. *Eur. J. Med. Chem.* **2021**, *220*, No. 113501.

(30) Sun, M.; Zhao, C.; Gfesser, G. A.; Thiffault, C.; Miller, T. R.; Marsh, K.; Wetter, J.; Curtis, M.; Faghih, R.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. Synthesis and SAR of 5-Amino- and 5-(Aminomethyl)benzofuran Histamine H3 Receptor Antagonists with Improved Potency. *J. Med. Chem.* **2005**, *48* (20), 6482−6490.

(31) Pourabas, B.; Banihashemi, A. Polymers with benzofuro-benzofuran structures. *Polym. Int.* **2002**, *51* (10), 1086−1099.

(32) Xu, J.; Nie, G.; Zhang, S.; Han, X.; Pu, S.; Shen, L.; Xiao, Q. Electrosyntheses of poly (2, 3-benzofuran) films in boron trifluoride diethyl etherate containing poly (ethylene glycol) oligomers. *Eur. Polym. J.* **2005**, *41* (7), 1654−1661.

(33) Liu, J.; Luo, Y.; Li, L.; Wang, G.; Wang, X.; Chen, Y.; Liu, B. Photovoltaic performance of 4, 8-Bis (2′-ethylhexylthiophene) thieno [2, 3-f] benzofuran-Based dyes fabricated with different donors in dye-sensitized solar cells. *ACS Omega* **2020**, *5* (21), 12440−12450.

(34) Carella, A.; Roviello, V.; Iannitti, R.; Palumbo, R.; La Manna, S.; Marasco, D.; Trifuoggi, M.; Diana, R.; Roviello, G. N. Evaluating the biological properties of synthetic 4-nitrophenyl functionalized benzofuran derivatives with telomeric DNA binding and antiproliferative activities. *Int. J. Biol. Macromol.* **2019**, *121*, 77−88.

(35) Tabassum, S.; Zahoor, A. F.; Ahmad, S.; Noreen, R.; Khan, S. G.; Ahmad, H. Cross-coupling reactions towards the synthesis of natural products. *Mol. Divers.* **2022**, *26*, 647−689.

(36) Dat, N. T.; Jin, X.; Lee, K.; Hong, Y. S.; Kim, Y. H.; Lee, J. J. Hypoxia-inducible factor-1 inhibitory benzofurans and chalcone-derived diels− alder adducts from Morus species. *J. Nat. Prod.* **2009**, *72* (1), 39−43.

(37) Yamatake, Y.; Shibata, M.; Nagai, M. Pharmacological studies on root bark of mulberry tree (Morus alba L.). *Jpn. J. Pharmacol.* **1976**, *26*, 461−469.

(38) Kim, E. S.; Park, S. J.; Lee, E. J.; Kim, B. K.; Huh, H.; Lee, B. J. Purification and characterization of Moran 20K from Morus alba. *Arch. Pharm. Res.* **1999**, *22*, 9−12.

(39) Andallu, B.; Suryakantham, V.; Lakshmi Srikanthi, B.; Kesava Reddy, G. Effect of mulberry (Morus indica L.) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes. *Clin. Chim. Acta* **2001**, *314* (1−2), 47−53.

(40) Song, P. S.; Tapley, K. J. Photochemistry and photobiology of psoralens. *Photochem. Photobiol.* **1979**, *29* (6), 1177−1197.

(41) Gasparro, F. P.; Dall'Amico, R.; Goldminz, D.; Simmons, E.; Weingold, D. Molecular aspects of extracorporeal photochemotherapy. *Yale J. Biol. Med.* **1989**, *62* (6), 579−593.

(42) Caffieri, S. Furocoumarin photolysis: chemical and biological aspects. *Photochem. Photobiol. Sci.* **2002**, *1*, 149−157.

(43) Santana, L.; Uriarte, E.; Roleira, F.; Milhazes, N.; Borges, F. Furocoumarins in medicinal chemistry. Synthesis, natural occurrence and biological activity. *Curr. Med. Chem.* **2004**, *11* (24), 3239−3261.

(44) Bickoff, E. M.; Booth, A. N.; Lyman, R. L.; Livingston, A. L.; Thompson, C. R.; Deeds, F. Coumestrol, a new estrogen isolated from forage crops. *Science* **1957**, *126* (3280), 969−970.

(45) Nevagi, R. J.; Dighe, S. N.; Dighe, S. N. Biological and medicinal significance of benzofuran. *Eur. J. Med. Chem.* **2015**, *97*, 561−581.

(46) Zahoor, A. F.; Kazmaier, U. A Straightforward Approach towards Functionalized γ-Hydroxy and Heterocyclic Amino Acids. *Synthesis* **2011**, *18*, 3020−3026.

(47) Irfan, A.; Zahoor, A. F.; Kamal, S.; Hassan, M.; Kloczkowski, A. Ultrasonic-assisted synthesis of benzofuran appended oxadiazole molecules as tyrosinase inhibitors: mechanistic approach through enzyme inhibition, molecular docking, chemoinformatics, ADMET and drug-likeness studies. *Int. J. Mol. Sci.* **2022**, *23* (18), 10979.

(48) Eldehna, W. M.; Al-Rashood, S. T.; Al-Warhi, T.; Eskandrani, R. O.; Alharbi, A.; El Kerdawy, A. M. Novel oxindole/benzofuran hybrids as potential dual CDK2/GSK-3β inhibitors targeting breast cancer: Design, synthesis, biological evaluation, and in silico studies. *J. Enzyme Inhib. Med. Chem.* **2021**, *36* (1), 271−286.

(49) Zhang, X.; Huang, H.; Zhang, Z.; Yan, J.; Wu, T.; Yin, W.; Sun, Y.; Wang, X.; Gu, Y.; Zhao, D.; Cheng, M. Design, synthesis and biological evaluation of novel benzofuran derivatives as potent LSD1 inhibitors. *Eur. J. Med. Chem.* **2021**, *220*, No. 113501.

(50) Nakaie, M.; Katayama, F.; Nakagaki, T.; Yoshida, S.; Kawasaki, M.; Nishi, K.; Ogawa, K.; Toriba, A.; Nishida, N.; Nakayama, M.; Fuchigami, T. Synthesis and Biological Evaluation of Novel 2-(Benzofuran-2-yl)-chromone Derivatives for In Vivo Imaging of Prion Deposits in the Brain. *ACS Infect. Dis.* **2022**, *8*, 1869−1882.

(51) Cao, X.; Qiu, D.; Zhang, R.; Li, Z.; Xu, X. Synthesis, nematicidal evaluation, and SAR study of benzofuran derivatives containing 2-carbonyl thiophene. *Chin. Chem. Lett.* **2023**, *34* (5), No. 107800.

(52) Coskun, D.; Dalkilic, S.; Dalkilic, L. K.; Coskun, M. F. The Synthesis, Characterization, and Anticancer Activity of New 2-acetylbenzofuran-Chalcone Hybrids. *Iran J. Sci. Technol. Trans. Sci.* **2021**, *45*, 1561−1569.

(53) Ashok, D.; Reddy, M. R.; Thara, G.; Dharavath, R.; Ramakrishna, K.; Nagaraju, N.; Gundu, S.; Sarasija, M. A new library of 1, 2, 3-triazole based benzofuran scaffolds: Synthesis and biological evaluation as potential antimicrobial agents. *J. Heterocycl. Chem.* **2022**, *59* (8), 1376−1384.

(54) Jin, L.-P.; Zhang, C.; Xie, Q.; Xu, J.; Wang, L.; Yang, L. C.; Huang, E.-F.; Wan, D. C.-C.; Hu, C. Design, synthesis and biological activity against estrogen receptor-dependent breast cancer of furo [1] benzofuran derivatives. *Arab. J. Chem.* **2022**, *15* (11), No. 104227.

(55) Abu-Hashem, A. A.; Hussein, H. A.; Aly, A. S.; Gouda, M. A. Synthesis of benzofuran derivatives *via* different methods. *Synth. Commun.* **2014**, *44* (16), 2285−2312.

(56) Heravi, M. M.; Zadsirjan, V. Recent advances in the synthesis of benzo [b] furans. *Adv. Heterocycl. Chem.* **2015**, *117*, 261−376.

(57) Bhargava, S.; Rathore, D. Synthetic routes and biological activities of benzofuran and its derivatives: a review. *Lett. Org. Chem.* **2017**, *14* (6), 381−402.

(58) Miao, Y. H.; Hu, Y. H.; Yang, J.; Liu, T.; Sun, J.; Wang, X. J. Natural source, bioactivity and synthesis of benzofuran derivatives. *RSC Adv.* **2019**, *9*, 27510−27540.

(59) Dwarakanath, D.; Gaonkar, S. L. Advances in synthetic strategies and medicinal importance of benzofurans: a review. *Asian J. Org. Chem.* **2022**, *11* (8), No. e202200282.

(60) Amin, A. Y.; Khassanov, A.; Reuter, K.; Meyer-Friedrichsen, T.; Halik, M. Low-voltage organic field effect transistors with a 2-tridecyl [1] benzothieno [3, 2-b][1] benzothiophene semiconductor layer. *J. Am. Chem. Soc.* **2012**, *134* (40), 16548−16550.

(61) Chen, D.; Yuan, D.; Zhang, C.; Wu, H.; Zhang, J.; Li, B.; Zhu, X. Ullmann-type intramolecular C−O reaction toward thieno [3, 2-b] furan derivatives with up to six fused rings. *J. Org. Chem.* **2017**, *82* (20), 10920−10927.

(62) Ma, W.; Huang, J.; Li, C.; Jiang, Y.; Li, B.; Qi, T.; Zhu, X. One-pot synthesis and property study on thieno [3, 2-b] furan compounds. *RSC Adv.* **2019**, *9*, 7123−7127.

(63) Ai, L.; Ajibola, I. Y.; Li, B. Copper-mediated construction of benzothieno [3, 2-b] benzofurans by intramolecular dehydrogenative C−O coupling reaction. *RSC Adv.* **2021**, *11*, 36305−36309.

(64) Akhtar, R.; Zahoor, A. F.; Rasool, N.; Ahmad, M.; Ali, K. G. Recent trends in the chemistry of Sandmeyer reaction: a review. *Mol. Divers.* **2022**, *26*, 1837−1873.

(65) Rao, M. L.; Islam, S. S. Copper-catalyzed synthesis of 1-(2-benzofuryl)-N-heteroarenes from o-hydroxy-gem-(dibromovinyl) benzenes and N-heteroarenes. *Org. Biomol. Chem.* **2021**, *19*, 9076−9080.

(66) Wu, W.; Luo, B.; You, Y.; Weng, Z. Copper-catalyzed one-pot synthesis of 2-(2, 2, 2-trifluoroethyl)-substituted benzofused heterocycles. *Org. Chem. Front.* **2021**, *8*, 1997−2001.

(67) Abtahi, B.; Tavakol, H. CuI-catalyzed, one-pot synthesis of 3-aminobenzofurans in deep eutectic solvents. *Appl. Organo. Chem.* **2021**, *35* (12), No. e6433.

(68) Ma, X.; Wang, Z.; Liu, Z.; Li, Z. One-Pot Three-Component Synthesis of 2-Methyl-3-aminobenzofurans Using Calcium Carbide as a Concise Solid Alkyne Source. *Chin. J. Chem.* **2021**, *39* (11), 2990−2994.

(69) Noreen, S.; Zahoor, A. F.; Ahmad, S.; Shahzadi, I.; Irfan, A.; Faiz, S. Novel chiral ligands for palladium-catalyzed asymmetric allylic alkylation/asymmetric Tsuji-Trost reaction: a review. *Curr. Org. Chem.* **2019**, *23* (11), 1168−1213.

(70) Canty, A. J.; Ariafard, A.; Malinakova, H. C. DFT characterisation of a Pd II→ I III adduct, and a Pd II complex formed after oxidative alkenylation of Pd II by [Ph (alkenyl) I III]+, in Pd-mediated synthesis of benzofurans involving Pd IV, annulation and chain-walking. *Dalton Trans.* **2022**, *51*, 9377−9384.

(71) Luo, H.; Wang, Z.; Chen, W.; He, C.; Zhang, G. Synthesis of 2-Benzoylbenzofurans *via* Palladium (II)-catalyzed Cascade Reactions. *Org. Prep. Proced. Int.* **2021**, *53* (2), 127−137.

(72) Qi, H.; Han, K.; Chen, S. Palladium-Catalyzed Aryl-Furanylation of Alkenes: Synthesis of Benzofuran-Containing 3, 3-Disubstituted Oxindoles. *J. Org. Chem.* **2021**, *86* (14), 9384−9395.

(73) Semwal, R.; Badhani, G.; Adimurthy, S. Pd-catalyzed annulation of imidazo [1, 2-a] pyridines with coumarins and indoles: synthesis of benzofuran and indole fused heterocycles. *Chem. Commun.* **2022**, *58* (10), 1585−1588.

(74) Wang, J. S.; Li, C.; Ying, J.; Xu, T.; Lu, W.; Li, C. Y.; Wu, X. F. Activated carbon fibers supported palladium as efficient and easy-separable catalyst for carbonylative cyclization of o-alkynylphenols with nitroarenes: Facile construction of benzofuran-3-carboxamides. *J. Catal.* **2022**, *413*, 713−719.

(75) Sun, J.; Ye, H.; Zhang, H.; Wu, X. X. Palladium-Catalyzed Cyclization Coupling with Cyclobutanone-Derived N-Tosylhydrazones: Synthesis of Benzofuran-3-Cyclobutylidenes and Spirocyclobutanes. *J. Org. Chem.* **2023**, *88*, 1568−1577.

(76) Reddy, G. S.; Shukla, S.; Bhuktar, H.; Hossain, K. A.; Edwin, R. K.; Giliyaru, V. B.; Misra, P.; Pal, M. Pd/Cu-catalyzed access to novel 3-

(benzofuran-2-ylmethyl) substituted (pyrazolo/benzo) triazinone derivatives: their in silico/in vitro evaluation as inhibitors of chorismate mutase (CM). *RSC Adv.* **2022**, *12*, 26686−26695.

(77) Li, Y.; Li, W.; Tian, J.; Huang, G.; Lv, H. Nickel-Catalyzed Asymmetric Addition of Aromatic Halides to Ketones: Highly Enantioselective Synthesis of Chiral 2, 3-Dihydrobenzofurans Containing a Tertiary Alcohol. *Org. Lett.* **2020**, *22* (14), 5353−5357.

(78) Zhu, X.-R.; Deng, C.-L. Nickel-Catalyzed Intramolecular Nucleophilic Addition of Aryl Halides to Aryl Ketones for the Synthesis of Benzofuran Derivatives. *Synthesis* **2021**, *53* (10), 1842−1848.

(79) Pinkert, T.; Das, M.; Schrader, M. L.; Glorius, F. Use of strain-release for the diastereoselective construction of quaternary carbon centers. *J. Am. Chem. Soc.* **2021**, *143* (20), 7648−7654.

(80) Kitano, J.; Nishii, Y.; Miura, M. Selective Synthesis of C4-Functionalized Benzofurans by Rhodium-Catalyzed Vinylene Transfer: Computational Study on the Cyclopentadienyl Ligand. *Org. Lett.* **2022**, *24* (31), 5679−5683.

(81) Söderberg, B. C. Transition metals in organic synthesis: Highlights for the year 2005. *Coord. Chem. Rev.* **2008**, *252*, 57−133.

(82) Zhu, H.; Zhou, Q.; Liu, N.; Xing, J.; Yao, W.; Dou, X. Relay Rhodium (I)/Acid Catalysis for Rapid Access to Benzo-2H-Pyrans and Benzofurans. *Adv. Synth. Catal.* **2022**, *364* (6), 1162−1167.

(83) Gong, X.; Yu, N.; Gu, L.; Li, Z.; Ma, W.; Zhao, F. Redox-neutral rhodium (iii)-catalyzed divergent synthesis of tetrasubstituted 1, 3-enynes and alkynylated benzofurans. *Org. Biomol. Chem.* **2022**, *21*, 147−152.

(84) Li, Y.; Tung, C. H.; Xu, Z. Synthesis of Benzofuran Derivates *via* a Gold-Catalyzed Claisen Rearrangement Cascade. *Org. Lett.* **2022**, *24* (31), 5829−5834.

(85) Hu, B. L.; Wu, C. F.; Zhang, X. G.; Kim, J. Direct synthesis of trifluoroethylated benzofurans from silver-catalyzed annulation of trifluoromethyl propynols with phenols. *Tetrahedron* **2022**, *121*, No. 132929.

(86) Hu, L.; Dietl, M. C.; Han, C.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Au−Ag Bimetallic Catalysis: 3-Alkynyl Benzofurans from Phenols *via* Tandem C− H Alkynylation/Oxy-Alkynylation. *Angew. Chem., Int. Ed.* **2021**, *60* (19), 10637−10642.

(87) Ouyang, L.; Lin, Z.; Li, S.; Chen, B.; Liu, J.; Shi, W. J.; Zheng, L. Synthesis of functionalized diarylbenzofurans *via* Ru-catalyzed C−H activation and cyclization under air: rapid access to the polycyclic scaffold of diptoindonesin G. *Org. Chem. Front.* **2021**, *8*, 6816−6822.

(88) Gao, J.; Fan, M.; Xiang, G.; Wang, J.; Zhang, X.; Guo, W.; Wu, X.; Sun, Y.; Gu, Y.; Ge, H.; Tan, R.; Qiu, H.; Shen, Y.; Xu, Q. Diptoindonesin G promotes ERK-mediated nuclear translocation of p-STAT1 (Ser727) and cell differentiation in AML cells. *Cell Death Dis.* **2017**, *8*, e2765−e2765.

(89) Kotha, S.; Solanke, B. U. Modular Approach to Benzofurans, 2H-Chromenes and Benzoxepines *via* Claisen Rearrangement and Ring-Closing Metathesis: Access to Phenylpropanoids. *Chem, Asian J.* **2022**, *17* (8), No. e202200084.

(90) Agar, O. T.; Cankaya, I. I. T. Analysis of phenylethanoids and their glycosidic derivatives. *Rec. Adv. Nat. Prod. Ana.* **2020**, 221−254.

(91) Greb, L. Lewis superacids: classifications, candidates, and applications. *Chem. Eur. J.* **2018**, *24* (68), 17881−17896.

(92) Raji Reddy, C.; Aila, M.; Subbarao, M.; Warudikar, K.; Grée, R. Domino Reaction of 2, 4-Diyn-1-ols with 1, 3-Dicarbonyl Compounds: Direct Access to Aryl/Heteroaryl-Fused Benzofurans and Indoles. *Org. Lett.* **2021**, *23* (12), 4882−4887.

(93) Lebold, T. P.; Kerr, M. A. Total Synthesis of Eustifolines A− D and Glycomaurrol *via* a Divergent Diels− Alder Strategy. *Org. Lett.* **2007**, *9* (10), 1883−1886.

(94) Liu, J.; Tian, M.; Li, A.; Ji, L.; Qiu, D.; Zhao, X. Acid-promoted selective synthesis of trifluoromethylselenolated benzofurans with Se-(trifluoromethyl) 4-methylbenzenesulfonoselenoate. *Tetrahedron Lett.* **2021**, *66*, No. 152809.

(95) Yang, C.; Li, Y.; Huang, Q.; Li, X. Lewis Acid Catalyzed [4+ 1] Cycloaddition of o-Quinone Methides and Isocyanides: Mild and Efficient Synthesis of 3-Aryl-2-aminobenzofurans. *Synlett* **2023**, *34* (11), 1230−1234.

(96) Lin, H.; Tang, S.; Pan, Y.; Liang, P.; Ma, X.; Jiao, W.; Shao, H. A Novel Method to Construct 2-Aminobenzofurans *via* [4+ 1] Cyclo-addition Reaction of In Situ Generated Ortho-Quinone Methides with Isocyanides. *Molecules* **2022**, *27* (23), 8538.

(97) Estopiñá-Durán, S.; Taylor, J. E. Brønsted Acid-Catalysed Dehydrative Substitution Reactions of Alcohols. *Chem. Eur. J.* **2021**, *27* (1), 106−120.

(98) Chen, X.; Lu, S.; Deng, P.; Chang, X.; Zhao, Y.; Ma, Y.; Zhang, D.; Xia, F.; Yang, L.; Wang, J.; Sun, P. Lewis Acid Regulated Divergent Catalytic Reaction between Quinone Imine Ketals (QIKs) and 1, 3-Dicarbonyl Compounds: Switchable Access to Multiple Products Including 2-Aryl-1, 3-Dicarbonyl Compounds, Indoles, and Benzofur-ans. *Adv. Synth. Catal.* **2022**, *364* (1), 94−102.

(99) Mandal, M.; Balamurugan, R. TfOH-promoted synthesis of indoles and benzofurans involving cyclative transposition of vinyl ketone. *Chem. Commun.* **2022**, *58*, 9778−9781.

(100) Pirouz, M.; Saeed Abaee, M.; Harris, P.; Mojtahedi, M. M. One-pot synthesis of benzofurans *via* heteroannulation of benzoquinones. *Heterocycl. Commun.* **2021**, *27* (1), 24−31.

(101) Yu, X. Y.; Chen, J. R.; Xiao, W. J. Visible light-driven radical-mediated C−C bond cleavage/functionalization in organic synthesis. *Chem. Rev.* **2021**, *121* (1), 506−561.

(102) Li, X.; Xu, Z.; Wang, L.; Wang, F.; Yang, J.; Li, P. A Facile Synthesis of Functionalized Benzofurans *via* Visible-Light-Induced Tandem Cyclization of 1, 6-Enynes with Disulfides. *ChemPhotoChem.* **2021**, *5* (2), 142−148.

(103) Liu, J.; Tang, S.; Wang, S.; Cao, M.; Zhao, J.; Zhang, P.; Li, P. Visible-Light-Induced 1, 6-Enynes Triggered C−Br Bond Homolysis of Bromomalonates: Solvent-Controlled Divergent Synthesis of Carbony-lated and Hydroxylated Benzofurans. *J. Org. Chem.* **2022**, *87* (14), 9250−9258.

(104) Koca, M.; Ertürk, A. S.; Bozca, O. Rap-Stoermer Reaction: TEA Catalyzed One-Pot Efficient Synthesis of Benzofurans and Optimiza-tion of Different Reaction Conditions. *ChemistrySelect* **2022**, *7* (30), No. e202202243.

(105) Zhang, Q.; Nie, H.; Zhang, K.; Huang, H.; Song, C. A novel base-promoted intramolecular cyclization approach for the synthesis of benzofurans, benzothiophenes and indoles. *Tetrahedron* **2022**, *116*, No. 132815.

(106) Wang, Z.; Cheng, L. C.; He, X.; Ye, K. Y. Lithium tert-butoxide/DMSO-mediated Rapid Synthesis of Naphthalenes, Benzofurans, and Indoles. *Asian J. Org. Chem.* **2023**, *12* (6), No. e202300135.

(107) Reddy, C. R.; Wadekar, K.; Nair, K.; Prapurna, Y. L. A Sequential Cycloisomerization/Oxidative Aromatization of 2-Prop-argyl-cyclohexenones for Direct Access to Substituted Benzofurans. *Synthesis* **2022**, *54* (20), 4503−4508.

(108) Yu, W.; Tung, C. H.; Xu, Z. Synthesis of Benzofurans from Sulfur Ylides and ortho-Hydroxy-Functionalized Alkynes. *Adv. Synth. Catal.* **2022**, *364* (21), 3749−3753.

(109) Ranjbari, M. A.; Tavakol, H. Catalyst-free synthesis of benzofuran derivatives from cascade reactions between nitroepoxides and salicylaldehydes. *J. Org. Chem.* **2021**, *86* (6), 4756−4762.

(110) Mundhe, P.; Bhanwala, N.; Saini, S. M.; Sumanth, G.; Shivaprasad, K.; Shende, S. U.; Reddy, K.; Chandrashekharappa, S. Domino synthesis of novel 3-alkenyl benzofuran derivatives-base mediated condensation cascade reaction. *Tetrahedron* **2023**, *132*, No. 133265.

(111) Doerner, C. V.; Scheide, M. R.; Nicoleti, C. R.; Durigon, D. C.; Idiarte, V. D.; Sousa, M. J. A.; Mendes, S. R.; Saba, S.; Neto, J. S. S.; Martins, G. M.; Rafique, J.; Braga, A. L. Versatile Electrochemical Synthesis of Selenylbenzo [b] Furan Derivatives Through the Cyclization of 2-Alkynylphenols. *Front. Chem.* **2022**, *10*, No. 880099.

(112) Kobayashi, A.; Matsuzawa, T.; Hosoya, T.; Yoshida, S. Synthesis of benzo [b] furans from alkynyl sulfoxides and phenols by the interrupted Pummerer reaction. *RSC Adv.* **2023**, *13*, 839−843.

(113) Liou, Y. C.; Wang, H. W.; Edukondalu, A.; Lin, W. Phosphine-Catalyzed Chemoselective Reduction/Elimination/Wittig Sequence for Synthesis of Functionalized 3-Alkenyl Benzofurans. *Org. Lett.* **2021**, *23* (8), 3064−3069.

(114) Lin, Z.; Tong, L.; Qiu, H.; Li, Z.; Shen, L.; Chen, N.; Yu, X. The Synthesis of 5-Hydroxybenzofurans *via* Tandem In Situ Oxidative Coupling and Cyclization. *SynOpen* **2022**, *6* (3), 158−163.

(115) Chen, D.; Fan, S.; Yang, Z.; Dai, J. Biocatalytic Application of a Membrane-Bound Coumarin C-Glucosyltransferase in the Synthesis of Coumarin and Benzofuran C-Glucosides. *Adv. Synth. Catal.* **2021**, *363* (22), 5072−5078.

(116) Tan, J.; Wang, R.; Xu, L.; Wu, W.; Deng, M.; Yuan, W.; Li, L.; Lin, Z. Synthesis of 2, 3-disubstituted Benzofuran *via* HNTf2/TMSOTf Catalyzed Intermolecular Reaction of o-alkenyl phenols and Aldehydes. *Adv. Synth. Catal.* **2023**, *365* (7), 983−989.