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Development of novel transition metal-catalyzed synthetic approaches for the synthesis of a dihydrobenzofuran nucleus: a review

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The synthesis of dihydrobenzofuran scaffolds bears pivotal significance in the field of medicinal chemistry and organic synthesis. These heterocyclic scaffolds hold immense prospects owing to their significant pharmaceutical applications as they are extensively employed as essential precursors for constructing complex organic frameworks. Their versatility and importance make them an interesting subject of study for researchers in the scientific community. While exploring their synthesis, researchers have unveiled various novel and efficient pathways for assembling the dihydrobenzofuran core. In the wake of extensive data being continuously reported each year, we have outlined the recent updates (post 2020) on novel methodological accomplishments employing the efficient catalytic role of several transition metals to forge dihydrobenzofuran functionalities.

1 Introduction

Dihydrobenzofuran scaffolds have been recognized as key structural motifs as they are an integral part of a vast range of biologically active compounds and have attracted significant consideration in the medicinal field.[1] The dihydrobenzofuran core is composed of two rings, *i.e.*, the aryl and dihydrofuran ring (Fig. 1). This unique structural feature makes them ideal candidates for the development of novel pharmaceutical agents.[2]

Owing to their high medicinal profile, the synthesis of various naturally occurring products containing a dihydrobenzofuran core has gained significant attention in organic and pharmaceutical chemistry.[3] Several bioactive natural products are composed of the 2,3-dihydrobenzofuran framework, such as (+)-decursivine **3**,[4] (+)-lithospermic acid **4**,[5] pterocarpan **5**,[6] (+)-conocarpan **6**,[7] bisabosqual A **7**,[8] and caraphenol A **8**,[9] which have been explored by several synthetic practitioners. They exhibit many biological activities such as anti-malarial, anti-HIV, hepatoprotective, anti-inflammatory and antifungal activities. Similarly, furaquinocins **9** (ref. 10) are also dihydrobenzofurans constituting natural products, which act as antihypertensive agents and inhibit platelet coagulation and aggregation. Furthermore, rubioncolin A **10** and rubioncolin B **12** are used to treat cough, uterine hemorrhage, bladder and kidney stones.[11] Cancer is one of the most prevailing and deadly diseases, and researchers are undertaking untiring efforts to discover and develop efficient anti-cancer agents.[12–16] (−)-Nocardione **11** (ref. 17) is a Cdc25B tyrosine phosphatase inhibitor that has been observed to display cytotoxic activities (Fig. 2).

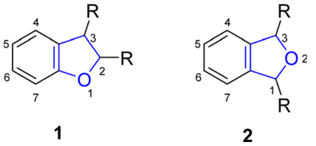

Fig. 1 General structure of dihydrobenzofuran **1** and dihydroisobenzofuran **2**.

Moreover, there are many synthetic dihydrobenzofuran derivatives demonstrating a variety of intriguing medicinal properties, including the imidazolium compound (cytotoxic) **13**,[18] diesters (anti-leishmaniasis) **14**,[19] GPR4 agonist **15**,[20] triazole (antitubercular) **16**,[21] and the drugs prucalopride **17** (used to treat constipation)[22] and efaroxan **18** (α_2-adrenoceptor antagonist)[23] (Fig. 3).

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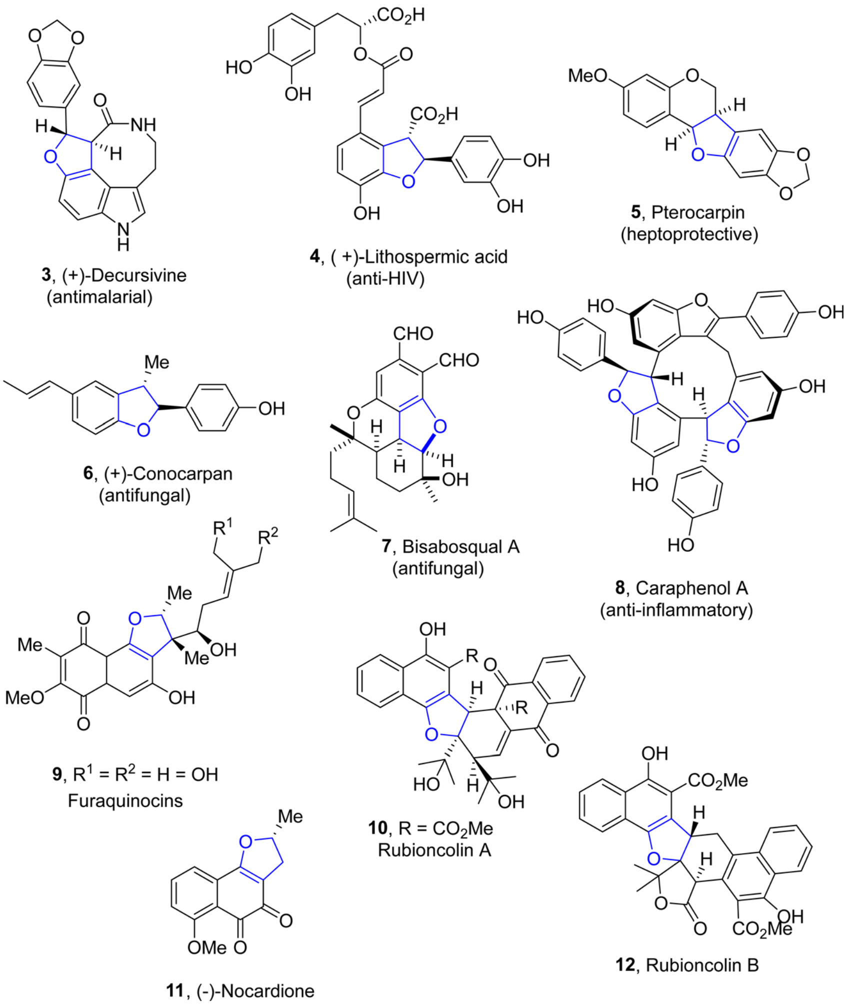


3, (+)-Decursivine (antimalarial)

4, (+)-Lithospermic acid (anti-HIV)

5, Pterocarpin (heptoprotective)

6, (+)-Conocarpan (antifungal)

7, Bisabosqual A (antifungal)

8, Caraphenol A (anti-inflammatory)

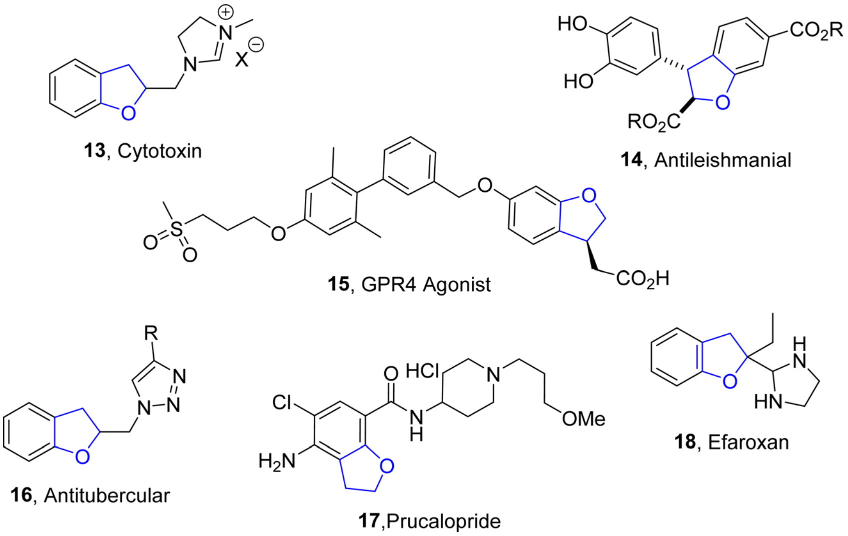
9, $R^1 = R^2 = H = OH$ Furaquinocins

10, $R = CO_2Me$ Rubioncolin A

11, (-)-Nocardione

12, Rubioncolin B

Fig. 2 Structures of some naturally occurring dihydrobenzofurans.



13, Cytotoxin

14, Antileishmanial

15, GPR4 Agonist

16, Antitubercular

17, Prucalopride

18, Efaroxan

Fig. 3 Structures of some synthetic dihydrobenzofurans.

There have been many processes reported for the synthesis of dihydrobenzofurans in the past decades that involve the use of different catalytic systems, *i.e.*, acid or base catalyzed synthesis,[24–26] organocatalysis,[27] salt catalyzed synthesis[28] as well as electrochemical and photochemical synthesis.[29,30] Transition metal (TM)-catalyzed reactions involving the synthesis of dihydrobenzofuran skeletons are one of the most reliable and beneficial methods.[31] In the past years, several synthetic researchers have designed and reported facile methodologies for the efficient synthesis of dihydrobenzofurans. In this regard, Blum[32] *et al.* in 2014 reported the Ru-catalyzed photochemical synthesis of dihydrobenzofuran derivatives **26** through the reaction of phenols **19** and alkenes **20** *via* oxidative [3 + 2] cycloadditions. Similarly, Fe-catalyzed facile generation of dihydrobenzofurans *via* the Claisen rearrangement of allyl aryl ethers **21** was reported by the research group of Sakate[33] in 2018. Furthermore, Henry and coworkers[34] in 2018 described an Fe and Cu dual catalysis protocol for the synthesis of 2,3-dihydrobenzofurans using substituted phenylethan-2′-ol **22**. Ir-catalyzed synthesis of 2,3-dihydrobenzofuran was reported by Ohmura and coworkers[35] in 2019, which proceeded *via* the intramolecular cycloaddition of the C–H bond of *o*-methyl ether **23** to the C–C double bond. In 2020, the research group of Fang[36] disclosed the efficient synthesis of chiral dihydrobenzofuran-3-ols *via* the Cu-catalyzed intramolecular reaction of aryl pinacol boronic esters **24**. In the same year, Li[37] *et al.* envisioned the Ni-catalyzed synthesis of chiral 2,3-dihydrobenzofurans using *ortho*-substituted aryl halides **25** (Fig. 4). In addition, multiple other TM-catalyzed approaches have also been reported in the literature.[38–40]

The TM-catalyzed synthesis of dihydrobenzofuran derivatives has gained tremendous interest in the field of organic chemistry as it exhibits high efficiency, *i.e.*, producing desired products in high yields under ambient reaction conditions.[41] Several reviews regarding the synthesis of dihydrobenzofurans have been published to date. In 2019, Laurita *et al.*[42] published a review on the synthesis of 2,3-dihydrobenzofurans covering the data from 2012 to 2019. Similarly, Dapkekar[43] *et al.* in 2022 also reported a review focusing on the methodological developments regarding the synthesis of dihydrobenzofurans and dihydroisobenzofurans. Besides all these published reviews, no particular review has been published concerning solely the TM-catalyzed synthesis of 2,3-dihydrobenzofurans. Herein, the recent data on the synthetic methodologies involving the TM-catalyzed synthesis of dihydrobenzofurans is summarized (reported within 2021–2024).

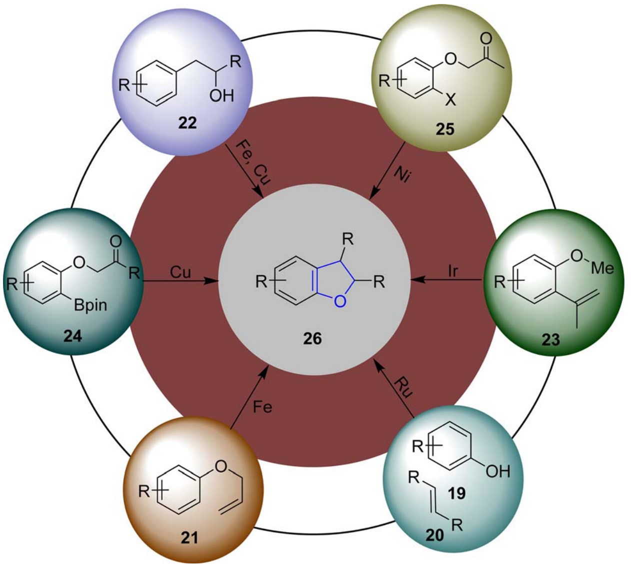


Fig. 4 Different transition metal-induced synthetic routes for the synthesis of dihydrobenzofurans.

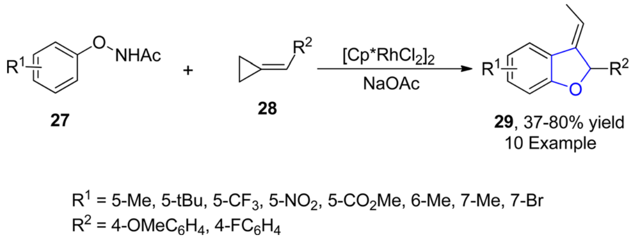
2 Review of literature

Transition metal-catalyzed transformations represent an advancing domain over the past few years. TM-mediated synthetic pathways have several advantages over conventional protocols.[44]

2.1. Rh-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Rhodium is one of the widely recognized metals in catalysis, which is extensively employed in organic synthesis and industrial processes. Among the range of synthetic methodologies represented for the synthesis of dihydrobenzofuran frameworks, Rh-catalyzed synthesis is a part of the most reliable approaches since they proceed under mild reaction conditions with high yield ranges. TM-catalyzed direct C–H bond functionalization has been proven as a powerful approach for the synthesis of target molecules in an unambiguous and step-economic way.[45] In particular, the combination of C–H bond functionalization with C–C bond activation to facilitate the rapid synthesis of functionally diverse frameworks from comparatively simple precursors has garnered considerable focus.[46] Considering the significance of utilization of TM-mediated C–H functionalization towards the synthesis of several heterocycles, Zhang[47] *et al.* in 2021 described the Rh(III)-catalyzed construction of cyclic 3-ethylidene-2,3-dihydrobenzofuran skeleton **29** with remarkable regioselectivity and chemoselectivity. In their novel approach, *N*-phenoxyacetamides **27** were reacted with cyclopropylidenemethyl alkenes **28** *via* subsequent C–H functionalization and [3 + 2] annulation in the presence of $[Cp^*RhCl_2]_2$ and NaOAc (as a base) to synthesize desired products **29** in moderate to high yields (37–80%) (Scheme 1).

In 2022, Song[48] *et al.* developed a novel protocol leading towards the synthesis of dihydrobenzofuran derivatives employing coupling partners associated *via* asymmetric C–H functionalization. In their methodology, substituted



Scheme 1 Synthesis of cyclic 3-ethylidene-2,3-dihydrobenzofuran **29**.

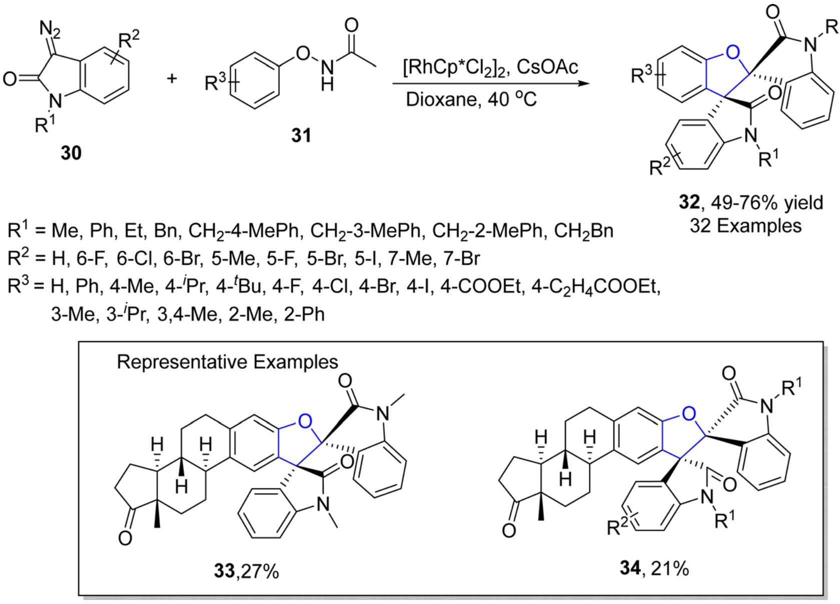
phenoxyacetamides **31** were made to react with diazooxindoles **30** in the presence of the rhodium-based catalyst (RhCp*Cl), exploiting cesium carbonate as a base in dioxane solvent. As a result, spirooxindoyl-substituted dihydrobenzofuran derivatives **32** were obtained in 49–76% yields (Scheme 2). The methodology was also employed for the synthesis of various heptacyclic molecules.

Sun[49] *et al.* in 2022 envisioned another rhodium-catalyzed difunctionalization of *p*-substituted olefinic arenes **35** to synthesize 2,3-dihydrobenzofuran derivatives **39**, **40** and **41**. Olefinic arenes **35** were made to react with unsaturated reactants such as isocyanates **38**, dioxazolones **37** and internal alkynes **36** *via* a tandem reaction. In their synthetic methodology, twofold C–H activation of **35** took place at the *ortho* and *meta* positions. In the first step, the already present directing group (DG) on **35** resulted in the installation of the alkene coupling partner on the *ortho* position. This further acted as a relayed directing group for the second activation of C–H, which resulted in the cyclization of olefins at the *para* position to form the desired products (benzofuran derivative) **39**, **40** and **41**. Moderate to high yields (40–86%) were obtained when the reaction was carried out in the presence of *t*-AmOH (as solvent), CsOPiv (as an additive), and AgOAc (as an oxidant) at 120 °C for 12 h (Scheme 3). The mechanism of the reaction was assumed to proceed *via* the interaction of olefinic arenes **35** with Rh catalyst. Further, alkyne insertion took place to generate intermediate **42**, followed by the dissociation of the bonds and C–H bond activation of intermediate **42**. In the next step, alkene insertion of **42** resulted in the formation of another intermediate **43**, which underwent reductive elimination to furnish the desired products **39** (Scheme 4). The synthetic utility of the above mentioned methodology was also examined.

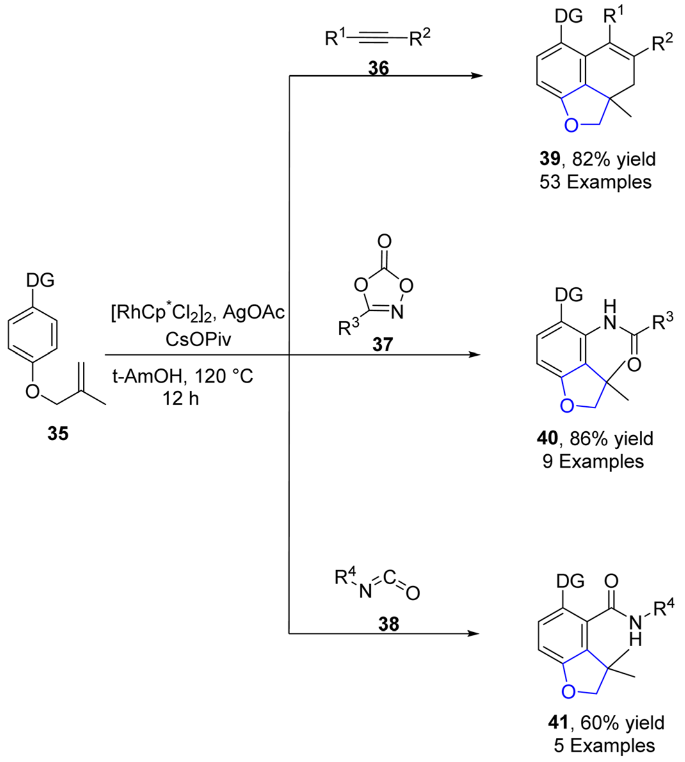
Wei[50] *et al.* in 2022 envisioned a rhodium-catalyzed [3 + 2] annulation of 2-alkenylphenols **44** and *N*-phenoxyacetamides **45** in the presence of base additive ($Zn(OAc)_2$) along with methanol (as a solvent) to access 2,3-dihydrobenzofurans **48** in excellent yields (90%). The proposed mechanism deduced that intermediate **46** was formed *via* reversible C–H/N–H bond cleavage of **45** assisted by Rh active catalyst, followed by the insertion of **44**, to furnish intermediate **47**. After subsequent oxidative addition, intramolecular hydrogen transfer and finally nucleophilic 1,4-addition gave the desired dihydrobenzofuran skeletons **48** (Scheme 5).

In the same year, another rhodium-catalyzed approach for the asymmetric synthesis of dihydrobenzofuran derivatives **51** was put forward by Yu[51] *et al.* In their methodology, aryl-joined alkenes **49** and substituted dioxazolone **37** were subjected to chiral rhodium-promoted carboamidation, using copper acetate as an additive in the presence of $AgSbF_6$ and dichloroethane to attain the enantioselective synthesis of dihydrobenzofurans **51** in 44–83% yield with up to 98.5 : 1.5 enantiomeric ratio. The reaction mechanism was proposed to undergo C–H activation and migratory insertion, followed by oxidative addition to generate intermediate **50**. The resulting intermediate **50** was then believed to execute reductive elimination and protonation to achieve enantioenriched 2,3-dihydro-3-benzofuranmethanamides **51** (Scheme 6). To examine the synthetic utility of this novel approach, derivatization of the synthesized compounds was also carried out.

Sinha[52] *et al.* in 2023 demonstrated a rhodium-promoted synthesis of dihydrobenzofurans **55**. Imidazole (directing group)-substituted allyloxy aryls **52** were subjected to intramolecular regioselective hydroarylation in the presence of $[RhCp^*Cl_2]_2$ catalyst, employing cesium acetate as a base in methanol : water (2 : 1) solvent. As a consequence, imidazole-constituting dihydrobenzofurans **55** were attained in moderate to excellent yield (52–91%). The reaction mechanism involved coordination with the rhodium catalyst, followed by



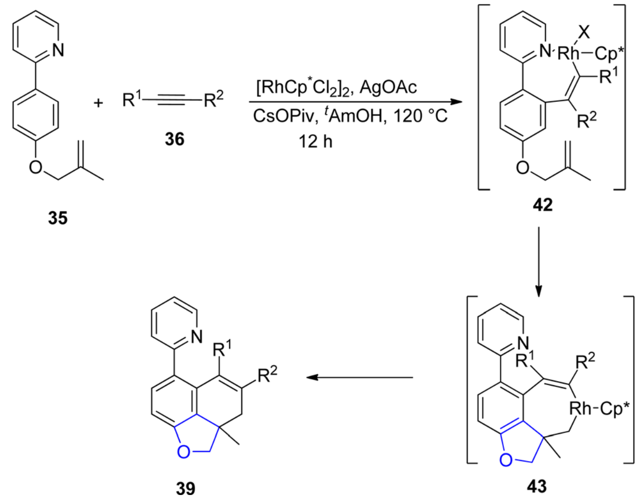
Scheme 2 Synthesis of bispirooxindoyl dihydrobenzofurans derivatives 32.



DG = 5-MePy, 5-OMePy, 5-FPy, 5-ClPy, 5-CF3, 4-MePy, 4-OMePy, 4-FPy, 4-ClPh, fused PhPy, pyridine
R^1 = 4-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 4-^{t}BuPh, 4-CF_3, 4-CO_2EtPh, 4-CNPh, 3-MePh, 3-OMePh,4 -FPh, 3-ClPh, 3-BrPh, 3-CO_2EtPh, Ph, $(Me)_2$Ph, 2-Naph, 2-furan, 2- thiophene, C_2H_4OTIPS, Me, Et, *n*-Pr, C_2H_4OMe, CH_2OMe
R^2 = 4-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 4-^{t}BuPh, 4-CF_3, 4-CO_2EtPh, 4-CNPh, 3-MePh, 3-OMePh,4 -FPh, 3-ClPh, 3-BrPh, 3-CO_2EtPh, Ph, $(Me)_2$Ph, 2-Naph, 2-furan, 2- thiophene,
R^3 = $PhCH_3$, $PhOCH_3$, Ph, Ph^{t}Bu, Naph
R^4 = $PhOCH_3$, $PhCH_3$, PhF, PhCl

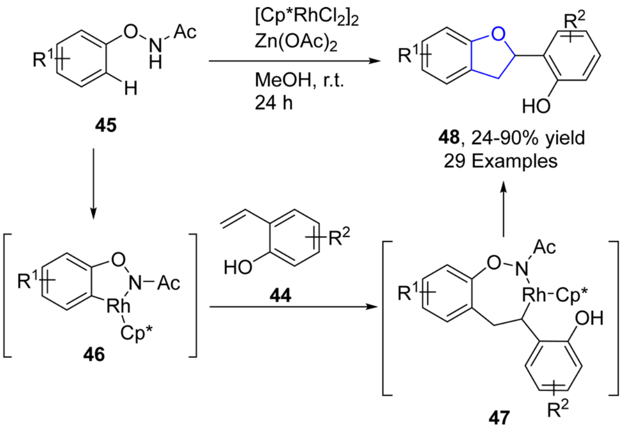
Scheme 3 Synthesis of diverse dihydrobenzofuran derivatives 39–41.

the activation of the C–H bond to generate rhodacycle intermediates **53** & **53***. The rhodacycle intermediate **53** was then supposed to undergo migratory insertion to generate the seven-membered intermediate **54**, which underwent contraction to furnish the target molecules **55** (Scheme 7).



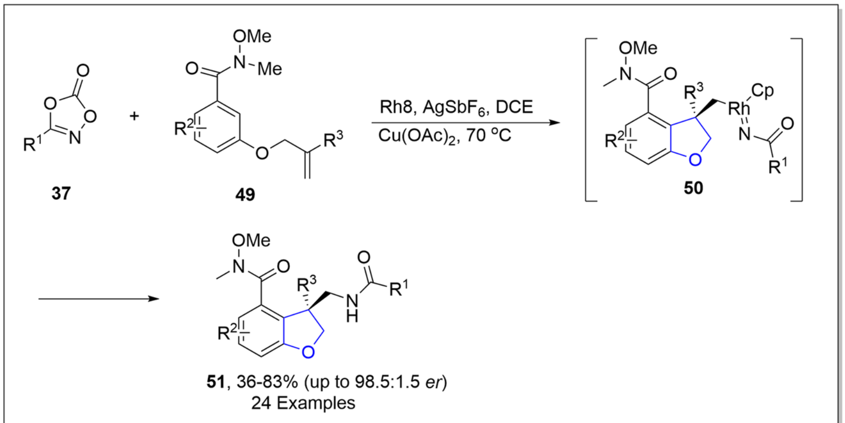
Scheme 4 Proposed mechanism for the synthesis of dihydrobenzofuran derivatives 39.

Oxa-Michael addition reaction is one of the significant reactions of Michael addition for the construction of C–O skeletons and is used for several methodological approaches towards dihydrobenzofurans synthesis.[53] In this regard, Zhu[54] *et al.* in 2021 accomplished the synthesis of diverse stereoisomers of asymmetric 2,3-dihydrobenzofurans **58**, **59**, **60** and **61** *via* one pot, stereodivergent dual catalysis. In their novel methodology, arylvinyldiazoacetates **56** were reacted with substituted aminophenols **57** in a relay catalytic system to synthesize asymmetric products (**58, 59, 60** and **61**) in excellent yields (up to 99%) with exceptional enantiomeric and diastereomeric excess (99% ee, 99 : 1 dr respectively). In this regard, an initial C–H functionalization was attained employing a rhodium catalyst consisting of ligand **64**, followed by the utilization of other organo-catalysts **62** and **63** that induced oxa-Michael addition to furnish the desired isomers of chiral 2,3-dihydrobenzofurans (**58, 59, 60** and **61**) (Scheme 8). In addition to gram scale synthesis, the derivatization of the generated products was also carried out as these compounds were transformed into pharmaceutically important and enantiopure amino alcohols.



R^1 = 5-Me, 5-^{t}Bu, 5-F, 5-Cl, 5-Br, 5-CO_2Me, 5-NO_2, 6-F,6-Cl, 7-Me, 7-Br, 5-CF_3, 5,6-fused C_4H_4, 5-C_2H_4NHBoc, H, 5,6-fused dodecahydro-3*H*-cyclopenta[*a*]naphthalen-3-one
R^2 = 3-CO_2Me, 3-NO_2, 3-F, 3-^{t}Bu, 3-Me, 3-Br, 4-F, 4-Cl, 3-tBu, 3-Cl, 5-C_2H_4NHBoc, H, 5,6-fused dodecahydro-3*H*-cyclopenta[*a*]naphthalen-3-one

Scheme 5 Synthesis of 2,3-dihydrobenzofuran derivatives **48**.



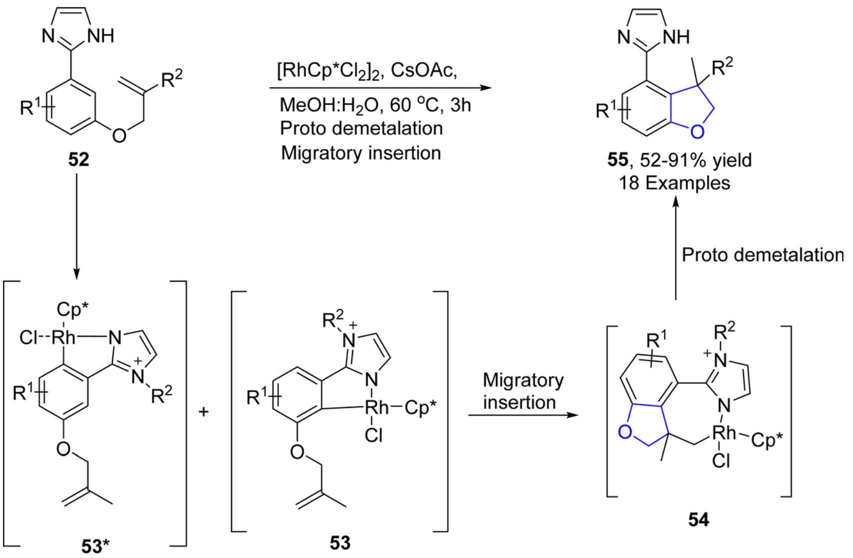
R^1 = 4-OMePh, Ph, 4-MePh, 4-FPh, naphthyl, furanyl, thiophenyl, Me, ^{t}Bu, tetrahydropyran
R^2 = 7-F, 7-Br, 7-Me, 7-MeO, 6-F, 6-Me, 7-(2-methyl)Ph, fused C_4H_4, fused $C_2H_4O_2$
R^3 = Me, Et, Ph, cyclopentyl, CH_2OBn

Scheme 6 Asymmetric synthesis of 2,3-dihydro-3-benzofuranmethanamides **51**.

Metal carbenes are diverse intermediates that enable particular C–C bond forming transformations including C–H insertion,[55] ylide formation,[56] and aromatic addition reactions.[57] The asymmetric synthesis of 2,3-dihydrobenzofurans involving the insertion of carbene precursors into C(sp^3)–H bonds potentially provides access to various crucial compounds like dihydrobenzofurans.[58] In this regard, in 2021, Bi[59] *et al.* designed a new method for the efficient assembly of asymmetric fluoroalkyl 2,3-disubstituted dihydrobenzofurans **66** in good to excellent yields (53–99%) with remarkable diastereomeric and enantiomeric ratio (>20 : 1 dr, 68 : 32–98 : 2 er) *via* a rhodium-catalyzed protocol. In their synthetic approach, fluoroalkyl *N*-triftosylhydrazones **65** were used as carbene precursors, which were transformed into the desired products **66** *via* the intramolecular insertion of carbene into the α-C(sp_3)–H bond of ether (Scheme 9). This efficient protocol was also used for the gram-scale synthesis of diverse 2,3-dihydrobenzofuran derivatives. Bi and coworkers also synthesized various enantioselective natural and bioactive molecules **67**, **68**, **69** and **70** employing the above methodology (Fig. 5).

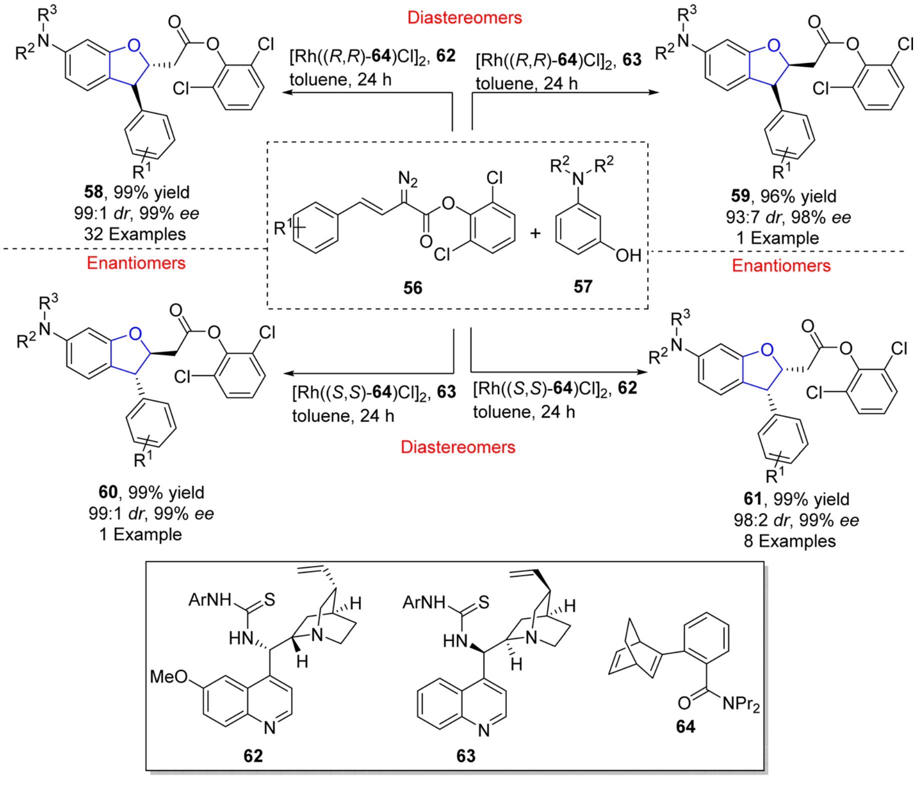
Buckley[60] *et al.* in 2021 reported the synthesis of novel diastereoselective dirhodium carboxylate catalysts and employed them in the construction of 2,3-dihydrobenzofuran skeletons **72**, **73**. In their novel methodology, the stereoselective C–H insertion reaction of aryldiazoacetates **71** took place in the presence of catalytic amount of dirhodium catalyst **74** to furnish 2,3-dihydrobenzofuran units **72** & **73** with excellent *trans* enantiopurity (84% ee) and *trans* diastereoselectivity (>91 : 9 dr) in toluene (Scheme 10).

In 2021, Hong[61] *et al.* accomplished the Rh and asymmetric phosphoric acid **79** catalyzed synthesis of 2,3-dihydrobenzofurans **78** *via* stereoselective Mannich type



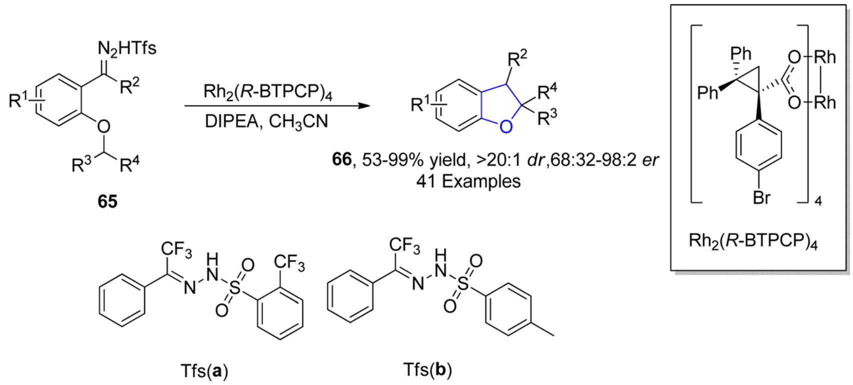
R^1 = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 5-OMe, 6-F, 6-Br, 6-I, 6-NO_2, 6-CF_3, 6-OMe
R^2 = Me, Et, ^{i}Pr, Ph, cyclohexyl

Scheme 7 Synthesis of imidazole-containing dihydrobenzofuran derivatives **55**.



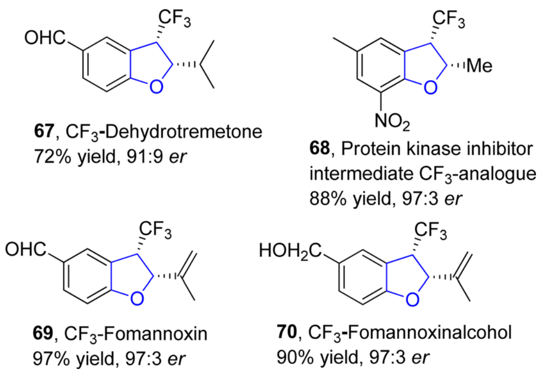
R^1 = 2-F, 3-OMe, 3-Me, 3-Br, 4-OMe, 4-Me, 4-Cl, 4-CF_3, 3,4-OMe, 3,5-diOMe, 3,4,5-triOMe, 3,4-fused C_4H_4, H, furanyl, thiophenyl
R^2 = R^3 = Me, Et, Bn, piperidine, pyrrolidine, morpholine, 1-benzylpiperazine, 1-benzylpyrrolidine, 1-(benzyloxy)piperidine, azepane

Scheme 8 Synthesis of asymmetric 2,3-disubstituted dihydrobenzofuran derivatives **58–61**.



R^1 = 5-Me, H, 5-Br, 6-OMe, 5-Cl, 5-NO$_2$
R^2 = CF$_2$CO$_2$Et, CF$_2$CO$_2$H, CF$_2$CONH$_2$, CF$_2$CO^{n}Bu, CF$_2$CH$_2$OH, CF$_2$CHO, CF$_2$CH$_2$OMe, CF$_2$CH$_2$SO$_3$Me, CF$_3$, CF$_2$CF$_3$
R^3 = H, Me, ^{n}C$_5$H$_{11}$, C$_2$H$_4$CO$_2$Me,
R^4 = Me, ^{n}C$_5$H$_{11}$, ^{n}C$_7$H$_{15}$, C$_2$H$_4$Ph, C$_3$H$_6$Cl, C$_2$H$_4$Br, C$_5$H$_7$, C$_3$H$_5$, CN, C$_2$H$_4$CO$_2$Me, CH$_2$OPh, Ph, 4-FC$_6$H$_4$, H, tetrahydro-2*H*-pyran, tetrahydrofuranyl, cyclopentyl, cyclopropyl, cyclobutyl, cyclohaxyl

Scheme 9 Synthesis of asymmetric fluoroalkyl dihydrobenzofurans **66**.



67, CF$_3$-Dehydrotremetone
72% yield, 91:9 *er*

68, Protein kinase inhibitor intermediate CF$_3$-analogue
88% yield, 97:3 *er*

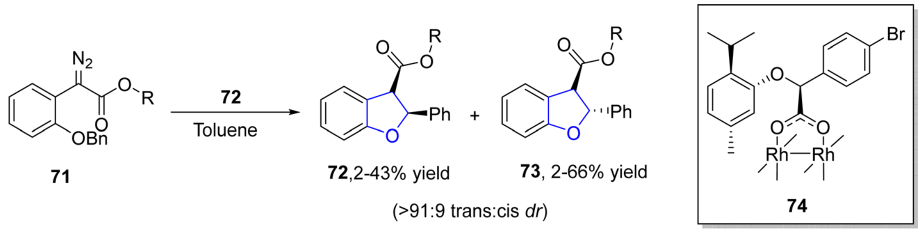
69, CF$_3$-Fomannoxin
97% yield, 97:3 *er*

70, CF$_3$-Fomannoxinalcohol
90% yield, 97:3 *er*

Fig. 5 Synthesized natural and bioactive molecules.

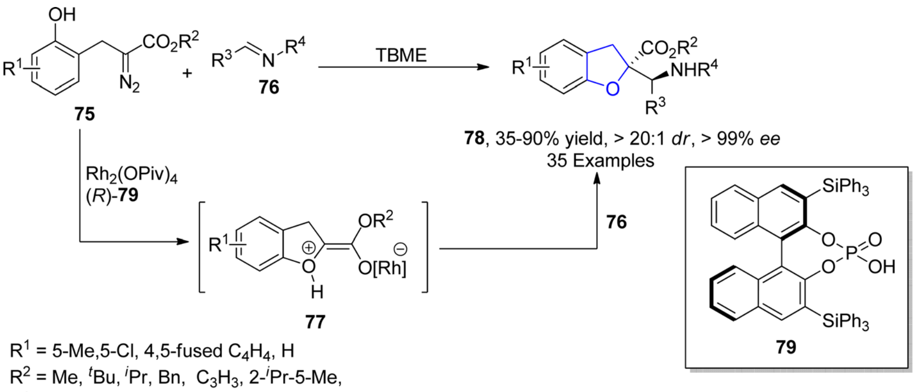
interception of phenolic oxonium ylides. In their novel methodology, diazo-containing phenolic derivatives **75** were made to react with imines **76** to synthesize the desired dihydrobenzofuran motifs **78** in low to excellent yield range (35–90%) with exclusive diastereoselectivity (>20 : 1 dr) and enantioselectivity (>99% ee) values. The formation of oxonium ylide intermediate **77** took place by the addition of phenolic OH, followed by the interception of **77** with imines **76** to generate Mannich-type products **78** in the presence of chiral phosphoric acid **77** (Scheme 11). Further transformations of the synthesized compounds were also carried out to demonstrate the synthetic efficacy of the mentioned approach.

In 2022, Hu[62] *et al.* presented a strategy for the efficient synthesis of 3-hydroxyoxindole incorporating 2,3-dihydrobenzofuran derivatives **83** *via* a Rh-catalyzed protocol. In their novel approach, diazo-containing phenolic compounds **80** were reacted with isatin **81** through an aldol type addition reaction to afford desired scaffolds **83** in moderate to excellent yields (58–98%) with exclusive diastereoselectivity (81 : 19–95 : 5 dr). Carbene species generated from diazo compound, underwent intramolecular cyclization with hydroxyl group to form oxonium ylide intermediate **82.** The isatin **81** added on the *Si*-face of **82** *via* aldol-type reaction to furnish desired 2,3-dihydrobenzofuran scaffolds **83** (Scheme 12). Two synthesized compounds **84** and **85** were found to exhibit anticancer activities against human colon cancer cells with 15.99 μM and 14.48 μM IC$_{50}$ values, respectively (Fig. 6). In order to demonstrate the practicality of the synthetic strategy, several spiro heterocyclic and amide products were



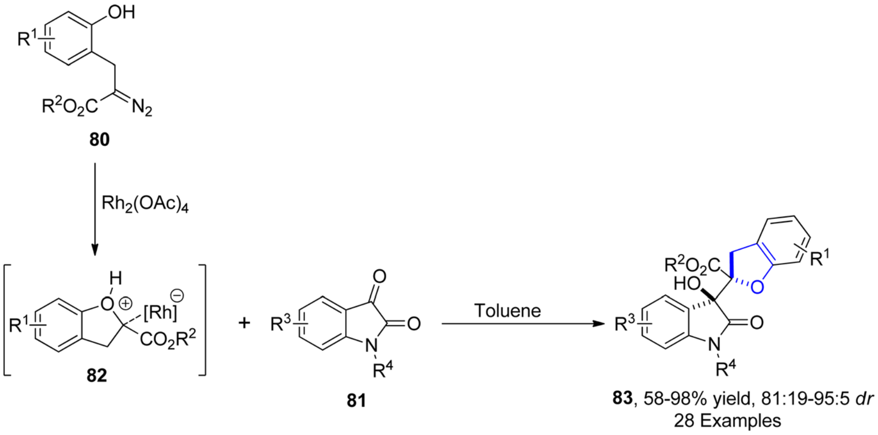
(>91:9 trans:cis *dr*)
R = Me, Bn, ^{i}Pr

Scheme 10 Synthesis of the 2,3-dihydrobenzofuran skeleton **72** and **73**.



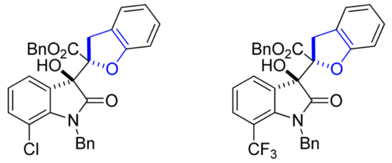
R^1 = 5-Me,5-Cl, 4,5-fused C_4H_4, H
R^2 = Me, ^{t}Bu, ^{i}Pr, Bn, C_3H_3, 2-^{i}Pr-5-Me,
R^3 = Ph, 4-FC_6H_4, 4-$CF_3C_6H_4$, 2-$CF_3C_6H_4$, 3-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-Cl-4C_6H_3, 4-AcC_6H_4, 4-$OMeC_6H_4$, 4-$CO_2MeC_6H_4$, thiophenyl, naphthyl, cyclohexyl, 1-methyl-1*H*-indole
R^4 = Ph, 4-$CF_3C_6H_4$, 4-$OMeC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4

Scheme 11 Synthesis of diastereoselective 2,2-disubstituted dihydrobenzofuran **78**.



R^1 = 5-F, 5-I, H
R^2 = ^{t}Bu, Bn, ^{i}Pr
R^3 = 6-Br, 4-Br, 4-Cl, 5-F, 5-Br, 5-I, 5-Me, 5-OMe, 6-OMe, 6-Cl, 7-F, 7-Cl, 7-CF_3, 5,7-Me,
R^4 = Me, CPh_3, Bn, CH_2-2-MeC_6H_4, C_3H_3, C_5H_9

Scheme 12 Synthesis of 3-hydroxyoxindole-containing 2,3-dihydrobenzofuran derivatives **83**.

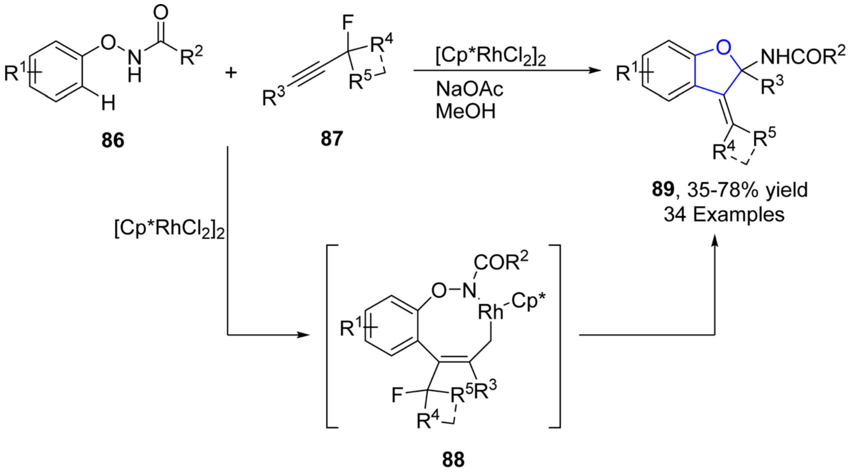


84, IC_{50} = 15.99 μM **85**, IC_{50} = 14.48 μM

Fig. 6 Structures of compounds **84** & **85** exhibiting anticancer potential.

also obtained from the synthesized 2,2-disubstituted dihydrobenzofurans **83**.

Rh-catalyzed synthesis of heterocycles *via* [3 + 2] annulation portray an appealing strategy as it offers complete regio- and stereo-control for introducing the functional groups. Related to that, Zhong[63] *et al.* in 2021 demonstrated the synthesis of α-quaternary carbon containing 2,3-dihydrobenzofuran analogues **89** *via* Rh-catalyzed C–H activation/[3 + 2] annulation. In their novel methodology, *N*-phenoxy amides **86** were reacted with propargylic monofluoroalkynes **87** in the presence of an Rh catalyst $[Cp^*RhCl_2]_2$ and NaOAc (used as base) to afford cyclic products **89** in low to high yields (35–78%). Rh-activated C–H activation of **87** took place, followed by the regioselective insertion of alkyne to afford the five-membered species **88.** Next, **88** subsequently underwent oxidative addition, reductive elimination and finally bimolecular nucleophilic substitution reaction to furnish 3-alkylidene-2,3-dihydrobenzofuran moiety **89** (Scheme 13). Various spiro compounds were also synthesized from these alkylidene-2,3-dihydrobenzofurans **89** to illustrate the synthetic utility of the reaction.



CP = Monoflourinated coupling partners

R^1 = 5-Me, 5-^{t}Bu, 5-F, 5-Cl, 5-Br, 5-I, 5-Ph, 5-CF_3, 5-CO_3Me, 5-CN, 5-NO_2, 6-OMe, 6-Me, 6-Cl, 7-Me, 7-Br, H, 5,6-fused C_4H_4

R^2 = Me, Et, ^{i}Pr, cyclopentyl

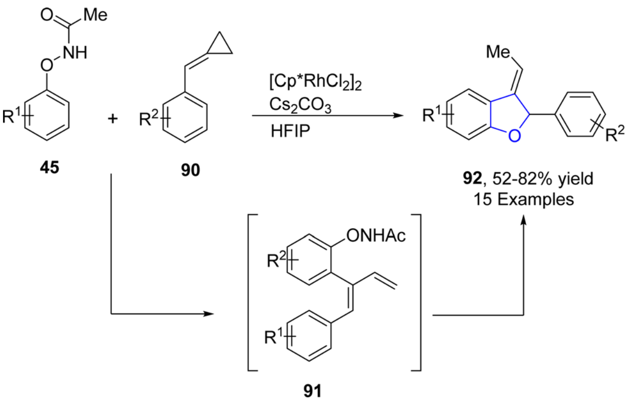
R^3 = 4-MeC_6H_4, 4-$^tBuC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CO_2MeC_6H_4$, 3-MeC_6H_4, 2-MeC_6H_4, Ph, Me, cyclopropyl

R^4 = Me, H, cyclobutyl, cyclopropyl

R^5 = Me, CH_2Bn, C_9H_{17}, cyclobutyl, cyclopropyl

Scheme 13 Synthesis of 3-alkylidene-2,3-dihydrobenzofurans **89**.

Singh[64] *et al.* in 2021 also reported the Rh-catalyzed, chemodivergent synthesis of 2,3-dihydrobenzofuran derivatives **92** through the coupling of *N*-phenoxyacetamides **45** with alkylidenecyclopropanes **90** *via* C–H and C–C bond activation. This transformation was in accordance with the fact that the cyclopropanes are highly reactive in nature and underwent ring opening reactions to give five-membered heterocyclic compounds.[65] Polar solvent, *i.e.*, hexafluoroisopropanol (HFIP), induced [3 + 2] annulation to achieve the desired products **92** in moderate to high yield (52–82%). Rh-assisted coupling of **45** and **90** took place, followed by the formation and scission of the 7-membered ring and subsequently β-hydride elimination to afford the intermediate **91**. Next, this intermediate **91** underwent the oxidative insertion of the N–O bond, nucleophilic addition and finally deprotonation to achieve 2,3-disubstituted dihydrobenzofuran derivatives **92** (Scheme 14). The gram scale synthesis was also performed in order to demonstrate the efficacy of the synthetic strategy.



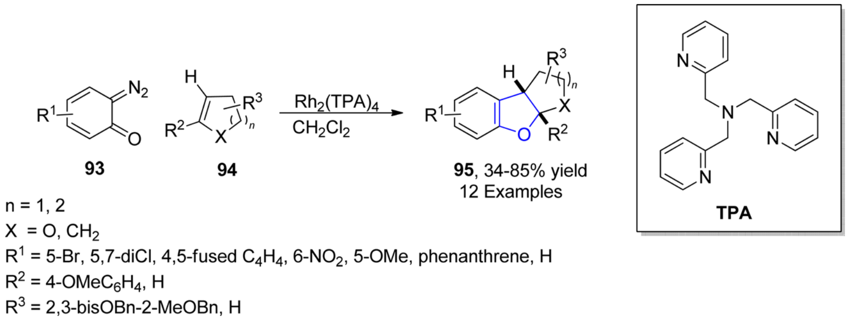
R^1 = 5-^{t}Bu, 5-Cl, 5-F, 5-Br, 5-CF_3, 6-Me, 7-Me, H

R^2 = 4-Me, 4-Cl, 4-Br, 4-Ph, 3,4-diOMe, 4-OH-3-OMe, 2-Me, 2,3-fused C_4H_4

Scheme 14 Synthesis of 3-ethylidenedihydrobenzofuran derivatives **92**.

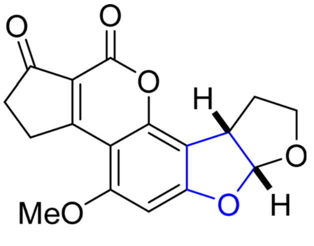
In 2021, Paymode and Sharma[66] designed a facile approach for the preparation of polycyclic 2,3-dihydrobenzofuran derivatives **95** *via* a rhodium-catalyzed system. In their synthetic approach, diazo compounds **93** were condensed with 2,3-dihydrofurans/cyclopentenes/cyclohexenes **94** *via* the [3 + 2] annulation process in the presence of $Rh_2(TPA)_4$ to furnish desired dihydrobenzofurans **95** in moderate to high yields (34–85%) (Scheme 15). In the wake of wide-spreading bacterial diseases, synthetic chemists have employed several synthetic pathways to develop efficacious anti-bacterial agents.[67] Employing the mentioned methodology, Paymode and Sharma also performed the total synthesis of naturally occurring aflatoxin B_2 **96a** (Fig. 7), which exhibits potent antimitotic and antimicrobial activities.

Various tailored molecules are synthesized as a result of ring-opening reactions of cyclic compounds.[68] Jiang[69] *et al.* in 2022 carried out the rhodium-mediated one pot synthesis of benzofuran-3(2*H*)-ones **101** by reacting aliphatic alcohols (MeOH) with salicylaldehyde **97** and cyclopropanols **98.** After interpreting the screening results, a total of three series of target heterocycles **101** were synthesized in moderate to high yield (32–70%) by independently adding the substitution on one of the three components one by one under optimized



Scheme 15 Synthesis of fused rings containing 2,3-dihydrobenzofuran derivative **95**.

conditions ([CpRhCl$_2$]$_2$ catalyst, Cu(OAc)$_2$ oxidant & CsOAc (additive) (Scheme 15). The reaction mechanism was proposed to involve the C–H activation of substituted salicylaldehydes **97**, followed by ligand exchange with aryl cyclopropanols **98**, β-carbon elimination and reductive elimination (cyclopropane ring opening) to result in C–H alkylation product **99**. The compound **99** was then supposed to be enolized by copper acetate, followed by β-hydride elimination and oxy-Michael addition to give benzofuranones **100**. Substituted benzofuranones **100** were then assumed to be reoxidized, followed by methanol involving Michael addition to afford target molecules **101** (Scheme 16).

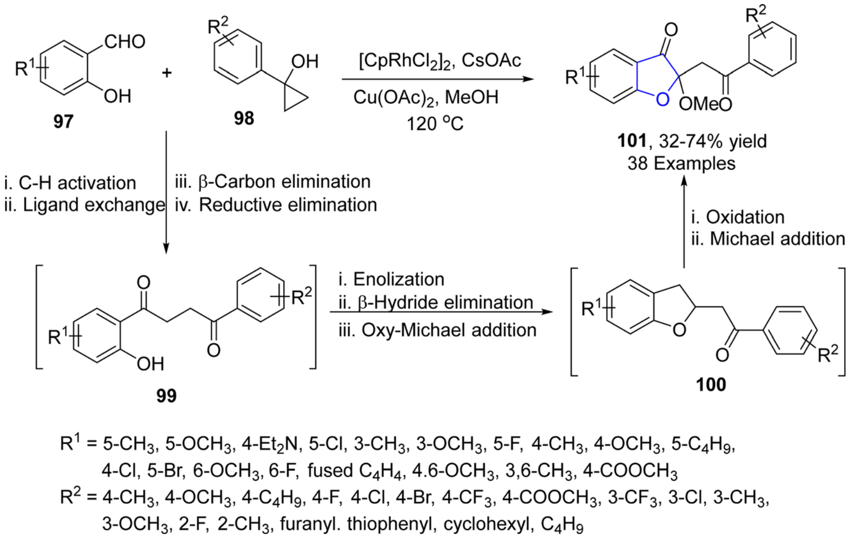


96a, Antimicrobial

Fig. 7 Structure of aflatoxin B$_2$ **96a**.

2.2. Pd-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

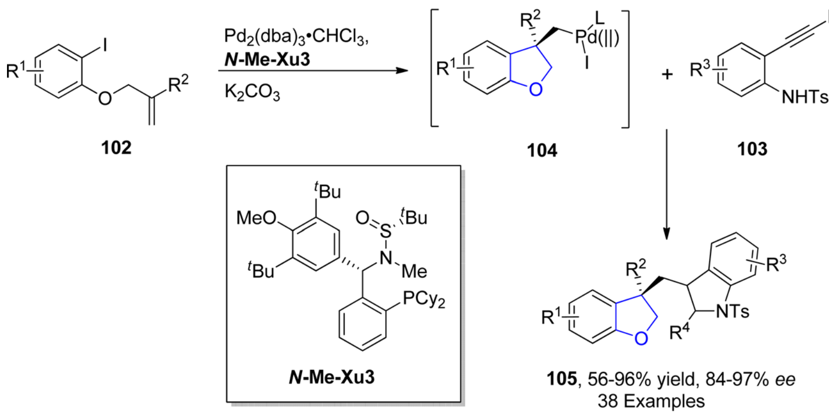
Palladium is a valuable gray-white metal, especially used as a catalyst due to its distinct properties such as thermal stability, resistance to poisoning, selectivity and its high surface area. Pd-catalyzed synthesis of five-membered heterocycles has been presented as the most beneficial and reliable synthetic methods as it has diverse functional group tolerance and carried out in mild reaction conditions.[70] The classical Heck coupling progresses through different steps including oxidative addition, proceeded by migratory insertion and reductive elimination. Heck coupling has provided novel methodologies towards the sophisticated aromatic substrates from organohalides and alkenes due to the stepwise development of synthetic logic.[71] Over the past few decennia, Pd-catalyzed Heck coupling has been widely used as one of the crucial synthetic tools facilitating the straightforward synthesis of molecular heterogeneity and complexity.[72] In 2021, Wu[73] *et al.* disclosed an enantioselective,



Scheme 16 Synthesis of benzofuran-3(2*H*)-ones **101**.

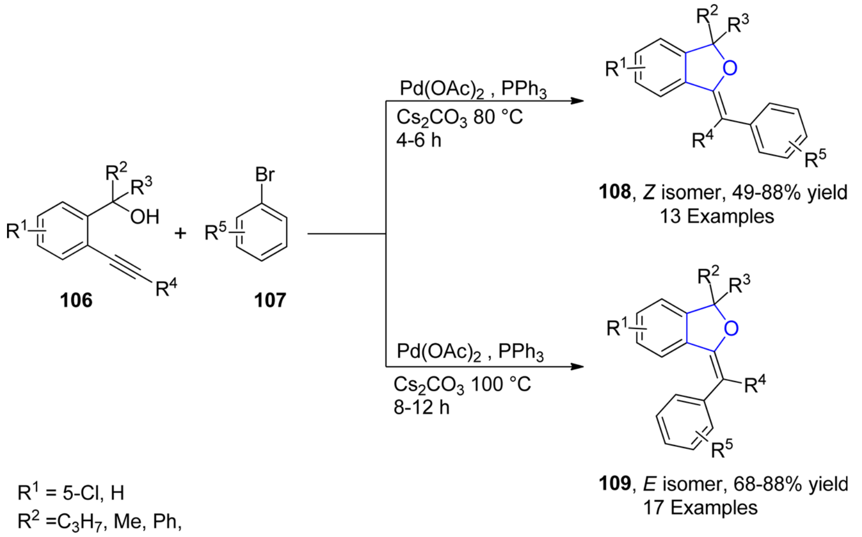
Pd-catalyzed method for the synthesis of 2,3-dihydrobenzofuran derivatives **105.** In their novel methodology, aryl iodide-joined alkenes **102** were reacted with *o*-alkynylanilines **103** in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ along with ligand *N*-Me–Xu$_3$ *via* Heck/Cacchi reactions to achieve dihydrobenzofurans in excellent yields (84–97%). Asymmetric σ-alkylpalladium intermediate **104** was formed *via* intramolecular Heck coupling reaction of Pd activated **102,** followed by its reaction with **103** to generate the desired polycyclic products **105** with exceptional enantiomeric excess (84–97% ee) (Scheme 17). The gram scale synthesis was also demonstrated along with the derivatization of the synthesized compounds.

In 2021, Sreenivasulu and Satyanarayana[74] envisioned a Pd-catalyzed, regio- and stereo-selective construction of *Z*/*E* isomers of 1,3-dihydroisobenzofurans **108** & **109** *via* the aryl Heck coupling of *o*-substituted tertiary alcohols **106** and substituted aryl bromides **107.** It is a temperature and time-dependent strategy, in which *Z*-isomer **108** was formed at 80 °C after 4–6 hours of reaction, whereas stable *E*-isomer **109** was attained at 100 °C after 8–12 hours of reaction (Scheme 18).



R^1 = 5-Me, 5-Ph 5-^{t}Bu, 5-C(Me)$_2$Ph, 5-F, 5-Cl, 5-Br, 5-NO$_2$, 5-CF$_3$, H, piperidin-1-yl methanone
R^2 = C_5H_{11}, C_2H_4Ph, ^{i}Pr, ^{t}Bu, C_3H_6-3-Me-1*H*-indole, CH$_2$TMS, Me, C_3H_6-benzo[*d*][1,3]dioxol-4-ol, C_3H_6-4,4-dimethylpiperidine-2,6-dione, C_3H_6-oxazolidin-2-one
R^3 = 5-OMe, 5-Me, 5-CN, 5-CF$_3$, 5-F, 5-Cl, 6-CO$_2$Me, H
R^4 = Ph, 4-OMeC$_6$H$_4$, 4-^{t}BuC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-CO$_2$MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-FC$_6$H$_4$, 3-OMeC$_6$H$_4$, PMP, C$_3$H$_6$Cl, ^{n}Bu, cyclohexyl, thiophene

Scheme 17 Synthesis of polycyclic dihydrobenzofurans **105**.



R^1 = 5-Cl, H
R^2 =C_3H_7, Me, Ph,
R^3 = Me, C_2H_5, C_3H_7, Ph, H
R^4 = C_5H_{11}, C_6H_{13}, C_8H_{17}, cyclopropyl
R^5 = 3-Me, 4-Me, 4-OMe, 2,3-fused C$_4$H$_4$, 3-Br, 4-COMe, 4-CHO, H, 4-NO$_2$, 3-F-4-NO$_2$, 4-((naphthalen-2-yloxy)methyl)benzonitrile

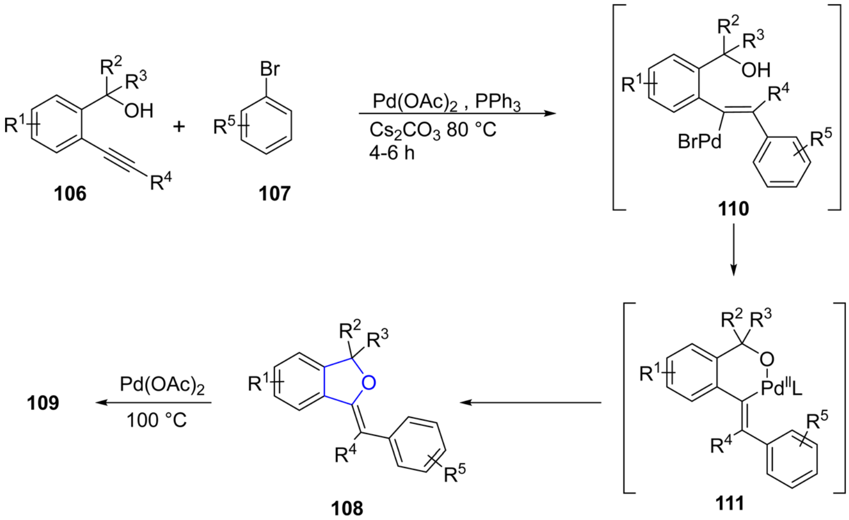
Scheme 18 Synthesis of (*Z*)/(*E*)-3-(1-arylalkylidene)-1,3-dihydroisobenzofurans **108** and **109**.

Initially, Pd-assisted intermolecular Heck coupling reaction between **106** and **107** took place to generate an intermediate **110**, followed by the elimination reaction to form a palladacycle **111**. Further, this palladacycle underwent intramolecular *oxo*-cyclization to furnish the desired heterocyclic products **108** & **109** in moderate to high yields, *i.e.*, 49–84% for *Z*-isomer and 68–88% for *E*-isomer, respectively (Scheme 19).

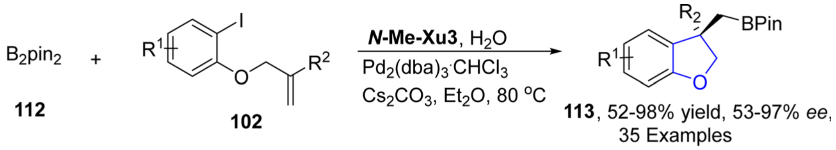
Pd/XuPhos catalyst is used as an efficient catalytic system for the stereodefined cascade Heck/intermolecular C–H alkylation reactions.[75] Taking into consideration the wide synthetic utility of borylated compounds, Wu[76] *et al.* in 2022, also developed a novel palladium promoted Heck/borylation strategy utilizing alkenes fused with aryl iodides **102** as precursors. Their synthetic protocol involved the treatment of aromatic rings substituted alkenes **102** and B_2pin_2 **112** in the presence of $Pd_2(dba)_3\cdot CHCl_3$ catalyst exploiting *N*-Me–Xu_3 as a ligand (having 3,5-di-*tert*-butyl-4-methoxyphenyl group), using cesium carbonate as a base in diethyl ether and water. This protocol resulted in the efficacious and enantioselective synthesis of dihydrobenzofuran based boronic esters **113** (52–98%) with excellent enantiomeric excess (53–97% ee). This highly efficient synthetic strategy also paved routes towards the accomplishment of chromane, indoline and indane boronic esters (Scheme 20).

In 2022, Guo[77] *et al.* successfully designed a new Pd-catalyzed method for the synthesis of substituted 3,3-disubstituted-2,3-dihydrobenzofurans *via* the reaction of olefin-tethered aryl iodides **102** with α,β-unsaturated ketones **114** and substituted styrenes **115**. In their one-pot synthetic methodology, two sequential Heck couplings took place, leading to the construction of dihydrobenzofuran skeletons **116** and **117**. Good to high yields, *i.e.*, 87% (**116**) and 78% (**117**), with exclusive *E*/*Z* selectivity (20 : 1) values of target molecules were achieved when $Pd(PhCN)_2Cl_2$ was subjected as a catalyst along with Cy_2NMe (base) in MeCN (solvent) (Scheme 21). The reaction mechanism was proposed to proceed *via* the reaction of reduced Pd species [Pd(0)] and aryl iodides **102** to form an intermediate **118**, which underwent subsequent intramolecular insertion reaction and olefin insertion reaction to form another intermediate **119**. Next, reductive elimination reaction finally generated the desired dihydrofuran products **117** (Scheme 22).

Spirocyclic organic compounds have acquired a significant place in medicinal chemistry due to their vast biological potential.[78] Marchese[79] *et al.* in 2022 devised a modular method for the preparation of 2,3-dihydrobenzofuran-based spirocyclic

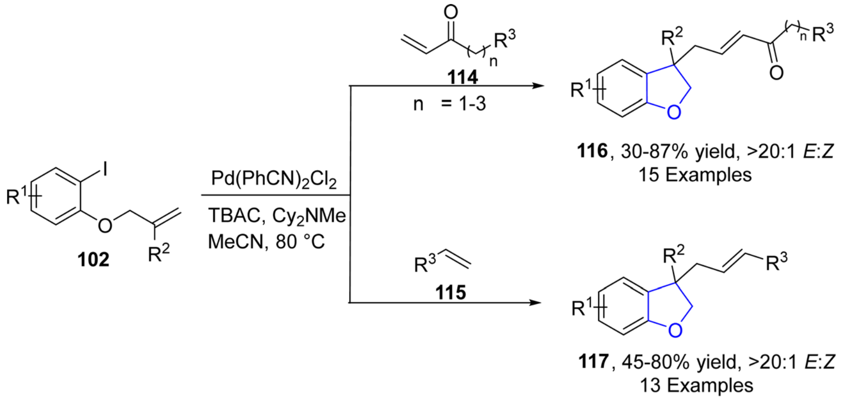


Scheme 19 Proposed mechanism for the synthesis of (*Z*)/(*E*)-3-(1-arylalkylidene)-1,3-dihydroisobenzofurans **108** and **109**.



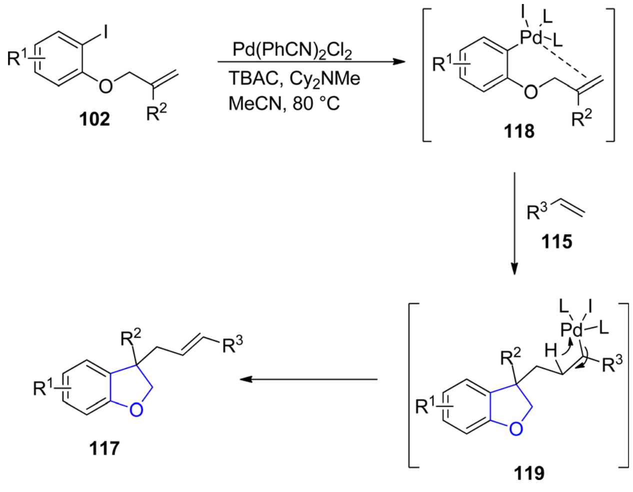
R^1 = 5-Me, 5-Ph, 6-^{t}Bu, fused C_4H_4, fused $C_2H_2NSO_2Ph$, 5-cumene, 5-F, 5-Cl
R^2 = Me, Et, ^{n}Pr, ^{n}Bu, ^{i}Pr, ^{t}Bu, Bn, 4-MePh, 4-FPh, 4-ClPh, 4-CF_3Ph, 3-FPh, 3-ClPh, 3-NO_2Ph, 3-MePh, 3-MeOPh, 3-^{t}BuPh, 2-MePh, 3,5-FPh, 3,4,5-FPh, naphthyl, CH_2-dibenzo[*b*,*d*]thiophene, CH_2TMS, $(CH_2)_4$Cl, $(CH_2)_4$-isoindoline -1,3-dione, CH_2-3-methyl-1*H*-indole, Ph

Scheme 20 Synthesis of 2,3-dihydrobenzofuranyl boronic esters **113**.



R^1 = H, 5-F, 5-Cl, 5-Br, 5-Me, 5-CF_3, 5-COOMe, 6-COOMe, 6-Cl, 6-Br, 4,5 fused C_6H_4,
6-1-(piperidin-1-yl)ethan-1-one
R^2 = Me,COOMe, COOEt, H
R^3 = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-CH3C_6H_4, 4-OCH3C_6H_4, 4-OPhC_6H_4, 4-tBu, 4-CF3C_6H_4,
4-NO_2, C_6H_5, 3-FC_6H_4, 2-FC_6H_4, naphthyl

Scheme 21 Synthesis of 3,3-disubstituted-2,3-dihydrobenzofuran **116** and **117**.



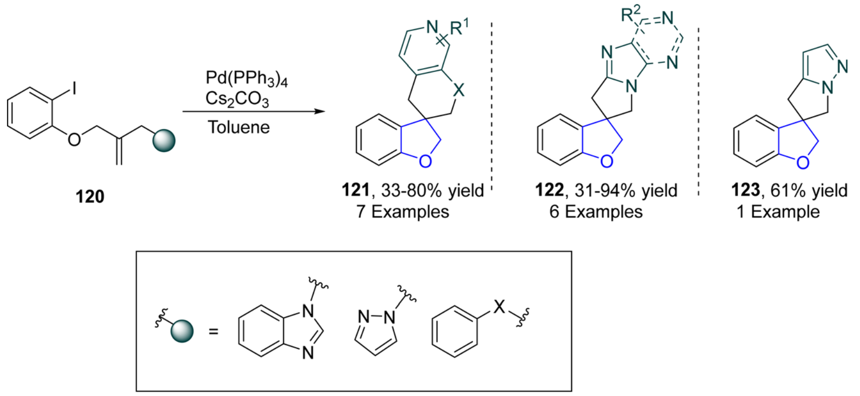
Scheme 22 Proposed mechanism for the synthesis of 3,3-disubstituted dihydrobenzofurans **117**.

compounds **121**, **122** and **123** *via* palladium catalysis. In their synthetic approach, *o*-substituted aryl iodides **120** were transformed into corresponding bis-heterocyclic spirocycles **121, 122** and **123** by following the Mizoroki–Heck-type reaction pathway in the presence of Cs_2CO_3 (used as base). Initially, the oxidative addition of **120** took place, followed by migratory insertion and C–H activation to form an intermediate, which on reductive elimination generated spirocyclic dihydrobenzofurans **121, 122** and **123.** Low to high yields (31–94%) were observed using this methodological approach (Scheme 23).

Another palladium-catalyzed method for dihydrobenzofurans was given by Kang[80] *et al.* in 2022. They carried out the palladium-mediated aminocarbonylation by treating aryl iodide-linked alkenes **124** with diversely substituted nitro compounds **125** and **126**. The reaction took place smoothly utilizing $PdCl_2$ as a catalyst, $Mo(CO)_6$ for the release of CO, triphenylphosphine as the ligand, DIPEA as base in tetrahydrofuran solvent without any addition of additive and reducing agent (Scheme 24). The synthetic pathway was proposed to follow the certain steps, *i.e.*, oxidative addition, intramolecular carbopalladation, linking and integration of CO to form intermediate **131.** This was followed by the attack of amine (obtained by the reduction of substituted nitro compound) and reductive elimination to gain dihydrobenzofuran derivatives **127** and **128** in 51–88% yields (Scheme 25).

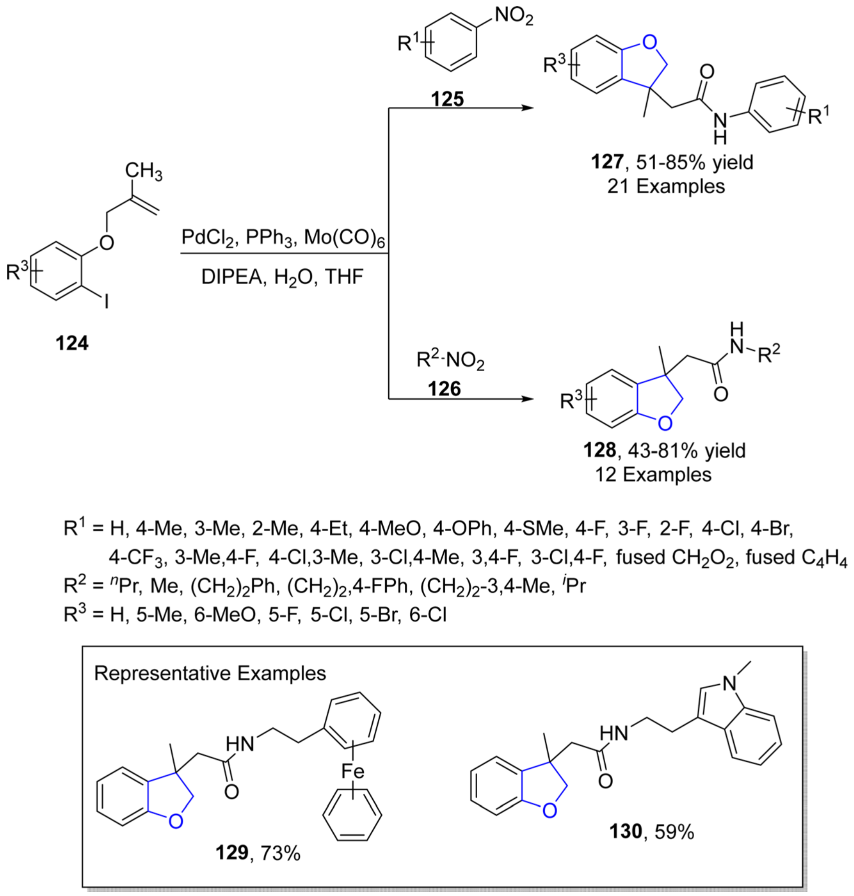
In 2023, another palladium-promoted asymmetric synthesis of dihydrobenzofurans *via* Heck/Tsuji–Trost was put forward by Zhang's group.[81] In the newly developed synthetic pathway, substituted dienes **133** were treated with halo-substituted phenols **134** using $Pd_2dba_3 \cdot CHCl_3$ as catalyst and TY-Phos as ligand using sodium phenoxide in dichloromethane, which afforded alkenyl-substituted dihydrobenzofurans **135** in 35–99% yield with enantiomeric excess (73–97 ee) (Scheme 26). To demonstrate the practicality of the novel synthetic approach, the gram scale synthesis of **135** was performed. Moreover, the derivatization of the synthesized compounds towards the synthesis of natural products, *i.e.*, tremetone and fomannoxin, was also performed.

The Pd-catalyzed synthesis of 2,3-dihydrobenzofurans involving the insertion of carbene precursors into C(sp^3)–H bonds potentially provides access to various crucial compounds like dihydrobenzofurans.[82] In 2023, Ding[83] *et al.* reported a rarely explored 1,5-Pd/H shift to synthesize dihydrobenzofurans. They treated alkynes-substituted compounds **136** (obtained from 2-bromo-3-hydroxy benzaldehydes) with R–B$(OH)_2$/R–BPin, substituted alkynols **137** and *N*-sulfonyl hydrazones **138** *via* palladium catalyzed ($PdCl_2$ & $Pd(OAc)_2$ respectively) cascade reaction. The reaction proceeded *via* the 1,5-Pd/H shift approach between the vinyl and acyl moiety to furnish acyl palladium species. The acyl palladium intermediates were then



X = O, NTs, N
R^1 = 7-CO_2Me, 7-Me, 8-Cl, 8-SO_2-4-MeC_6H_4, H
R^2 = 4-Cl, H

Scheme 23 Synthesis of heterocyclic spiro-2,3-dihydrobenzofurans **121**, **122** and **123**.

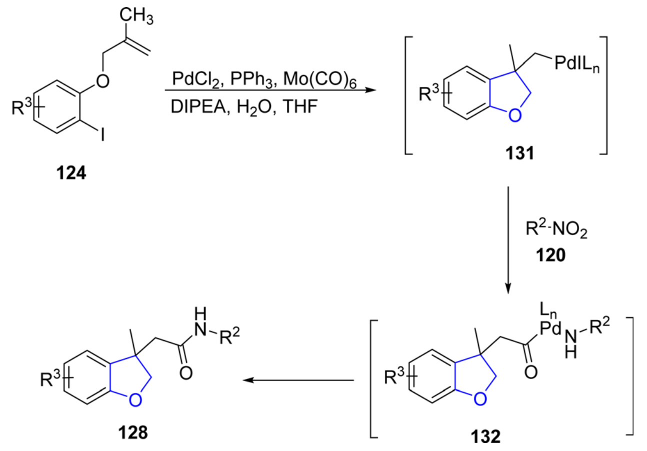


R^1 = H, 4-Me, 3-Me, 2-Me, 4-Et, 4-MeO, 4-OPh, 4-SMe, 4-F, 3-F, 2-F, 4-Cl, 4-Br, 4-CF_3, 3-Me,4-F, 4-Cl,3-Me, 3-Cl,4-Me, 3,4-F, 3-Cl,4-F, fused CH_2O_2, fused C_4H_4
R^2 = ^{n}Pr, Me, $(CH_2)_2$Ph, $(CH_2)_2$,4-FPh, $(CH_2)_2$-3,4-Me, ^{i}Pr
R^3 = H, 5-Me, 6-MeO, 5-F, 5-Cl, 5-Br, 6-Cl

Scheme 24 Synthesis of carbamoyl-substituted 2,3-dihydrobenzofurans **127** and **128**.

subjected to decarbonylation, followed by the reaction with nucleophiles to yield dihydrobenzofuran derivatives **139, 140** and **141** in efficient yields *via* decarbonylative alkenylation, arylation and alkynylation (Scheme 27). The novel synthetic strategy highlights the significant synthetic efficacy, facilitating the production of disubstituted and polycyclic products.

Annulation reactions simply refer to the process of combining two or more molecular fragments, often cyclic structures, to form bridged or fused ring systems. Pd-catalyzed annulation reactions involving the synthesis of arene-fused furan heterocycles have tremendous importance in organic synthesis.[84] In this perspective, Zhou[85] *et al.* in 2021 prepared



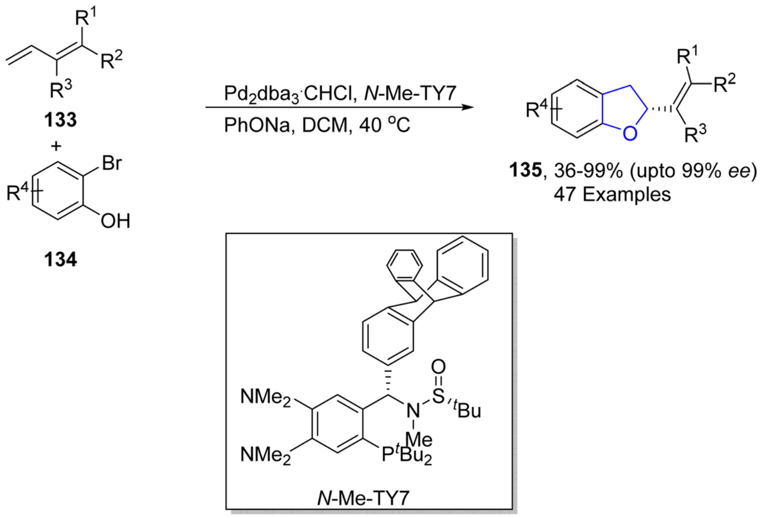
Scheme 25 Proposed mechanism for the synthesis of carbamoyl-substituted 2,3-dihydrobenzofurans **128**.

a library of polycyclic dihydrobenzofurans **146** *via* Pd-catalyzed annulation reaction. In their novel methodology, alkenyl ethers **142** and alkynyl oxime ethers **143** underwent cyclization reaction in the presence of $Pd(OAc)_2$ along with $CuCl_2$ (used as an oxidant) and tetrabutyl ammonium bromide (as co-catalyst) to afford 2,3-dihydrobenzofuran derivatives **146** in moderate to excellent yields (41–86%) (Scheme 28). This synthetic approach covers a broad range of substrate scope (32 examples). Various synthetic transformations of the synthesized compounds took place to illustrate the synthetic efficiency of the procedure.

Similarly, in 2022, Houghtling[86] *et al.* reported a palladium-catalyzed protocol for the synthesis of variety of dihydrobenzofuran derivatives **148**, in which a novel urea ligand **149** was utilized to enhance the product yield (50–72%). In this context, substituted 2-bromophenols **134** were treated with 1,3-dienes **147** in the presence of NaO^tBu (as base) in a 9 : 1 ratio of PhMe and anisole (used as solvent) at 110 °C (Scheme 29).

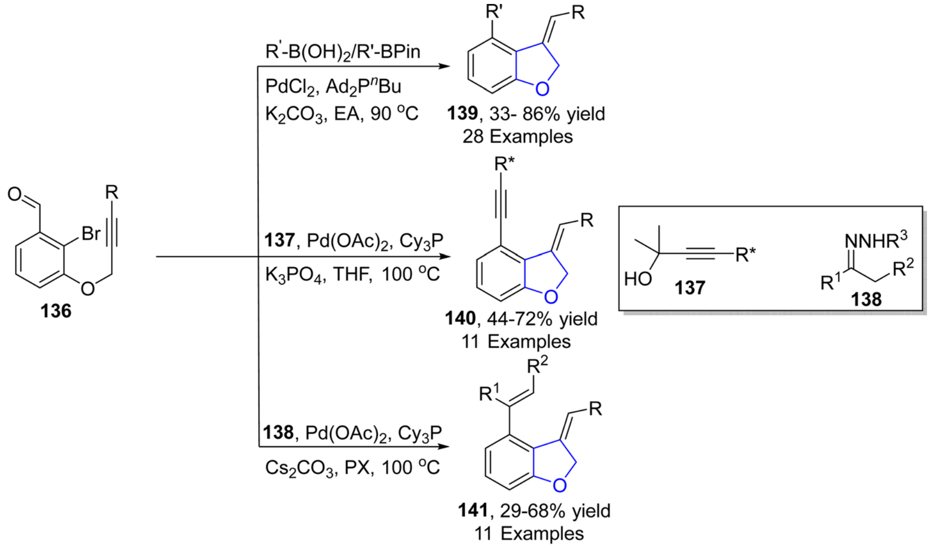
In 2023, Sun[87] *et al.* reported the palladium-catalyzed chiral [4 + 1] cyclization reaction to synthesize enantioselective dihydrobenzofurans **152.** In their synthetic methodology, cyclic vinyl methylene ketone **151** and leaving group substituted aryl ethers **150** were subjected to a series of allylation reaction and C–H activation reaction in the presence of palladium catalyst and ligand **L**, utilizing cesium fluoride as a base in 2-methyl tetrahydrofuran and acetone. As a result, the enantiomeric synthesis of a library of dihydrobenzofurans **152** was achieved in 38–89% yield up to 99 : 1 enantiomeric ratio. The reaction mechanism was supposed to involve the palladium mediated decarboxylation of substituted vinyl methylene carbonate, oxidative process, O-nucleophilic conversion, asymmetric concerted metalation–deprotonation, protonation and reductive elimination to yield target molecules (Scheme 30). Various derivatives of **152** were synthesized in order to elaborate the synthetic efficiency.

In recent times, synthesis of various heterocycles and carbocycles have been achieved by employing alkyne cyclization. In these cyclization reactions, palladium-based catalysts have gained great significance. In 2023, Sun[70] *et al.* reported the synthesis of dihydrobenzofurans **145** by treating tosyl



R^1 = H, Ph, 2-MeOPh, 2-MePh, 2-CF_3Ph, 3-MePh, 3-ClPh, 4-OMePh, 4-OCF_3Ph, 4-^{t}BuPh, 4-PhC_6H_4, 4-ClPh, 4-CF_3Ph, 2,4,6-MePh, naphthyl, thiophenyl, cyclohexyl, C_2H_4Ph, $C_2H_2(CH_2)_{10}$Br, $C_2H_2C_5H_{11}$, $C_2H_2(CH_2)_5$OTBS, (*R*)-4,8-dimethylnona-1,7-diene, OTBS, fused C_4H_6,
R^2 = H, Me R^3 = H, Me
R^4 = 4-Me, 4-F, 5-OMe, 5-^{t}Bu, 5-Me, 5-F, 5-CF_3, 6-OMe, 6-Me, 6-F, 6-COOMe, 7-OMe, 7-Me, 7-Ac, fused C_4H_4

Scheme 26 Synthesis of 2,3-dihydrobenzofurans **135**.



R = Ph, 4-COOMePh, 4-CNPh, 4-OMePh, thiophenyl, TMS, Me, 4-OMePh
R' = Ph, 4-MePh, 4-ClPh, 4-COOMePh, 4-NPh$_2$Ph, 4-SiMe$_3$Ph, 2- COOMePh, 3,5-^{t}Bu, 3.5-OMe, fused CH$_2$O$_2$, 1,9-dihydropyrene, *tert*-butyl 1*H*-indole-1-carboxylate, furanyl, pyrimidine, 1-methyl-1*H*-pyrazole, C$_2$H$_2$Ph, C$_2$H$_2$Me, 3,6-dihydro-2*H*-pyran, 1,4-dioxaspiro[4.5]dec-7-ene, 4-OMePh, dibenzo[*b*,*d*]furan
R* = Ph, 4-OMePh, 2-COOMePh, 2-pyridyl, C$_2$Ph, cyclopropyl, ^{n}Bu, TIPS, α-Tocopherol
R^1 = Ph, 4-OMePh, 4-COOMePh, 4-ClPh, 2-MePh,
R^2 = H/ R^1 & R^2 = naphthyl, 1,2-dihydronaphthalene, indene, 6,7-dihydro-5*H*-benzo[7]annulene,
R^3 = 4-CF$_3$PhSO$_2$

Scheme 27 Synthesis of 2,3-dihydrobenzofurans **139–141**.

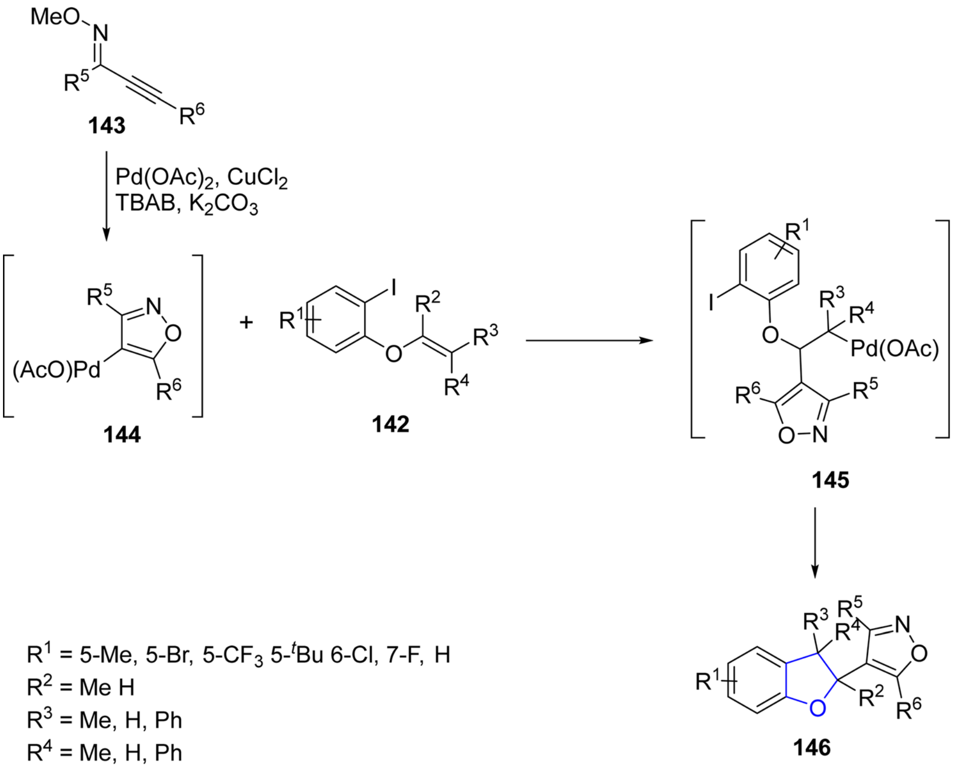
hydrazones **143** and aryl-substituted joined alkynes **144** in the presence of bis(triphenylphosphine)palladium(II) dichloride catalyst, using Cs$_2$CO$_3$ as a base and tricyclohexylphosphine PCy$_3$ as a ligand in toluene, followed by the addition of dienophile, *i.e.*, dimethylbut-2-ynedioate. The reaction mechanism involved the intramolecular carbopalladation, migratory insertion, γ-hydride elimination and Diels–Alder ([4 + 2] cycloaddition) reaction to furnish the spirocyclobutane-substituted dihydrobenzofurans **145** (Scheme 31).

Wu[88] *et al.* in 2021 developed a Pd-catalyzed protocol for the synthesis of 2,3-dihydrobenzofuran derivatives **158** *via* C(sp^3)–H and C(sp^2)–H intramolecular coupling. In their novel methodology, alkyl phenyl ethers **156** were used as efficient starting materials, which underwent subsequent C(sp^3)–H and C(sp^2)–H bond activation and reductive elimination in the presence of 1,4-dibenzoquinone (BQ), AgOAc and LiOAc (as base) to furnish desired heterocyclic products **158** in moderate to excellent yields (33–99%) (Scheme 32). The developed protocol was also utilized further for the gram scale synthesis of target molecules.

Reddy[89] *et al.* in 2021 proposed a Pd-catalyzed highly efficient protocol for the preparation of 2,2,3-trisubstituted dihydrobenzofuran derivatives **162** *via* intramolecular condensation. In their novel methodology, 2-hydroxyphenyl-substituted enones **159** were reacted with diazo compound **160** in the presence of [Pd(cinnamyl)Cl]$_2$ along with MeSO$_3$H (used as an additive) to afford dihydrobenzofurans **162** in moderate to excellent yields (51–91%). Active Pd catalyst interacted with diazo compounds **160** to give carbene species, which on nucleophilic addition with **159** gave oxonium ylides that existed in equilibrium with the corresponding zwitterions **161**. Zwitterions **161** were then trapped *via* Michael addition to afford desired products **162** (Scheme 33). Further, a number of substituted dibenzofuran products were also synthesized in order to demonstrate the synthetic efficiency of the novel approach.

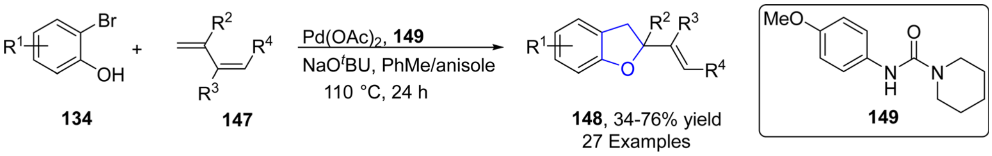
2.3. Cu-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Copper-based catalysts are most active, cheap and widely used catalysts in organic transformations and have various oxidation states. The reductive elimination of Cu(III) to generate C–X (X = heteroatom) bond is well studied in the literature.[90] Cu-catalyzed synthesis also plays a crucial role in the synthesis of diverse dihydrobenzofuran scaffolds.[91] Synthesis *via* deconstructive insertion reaction involving the generation of new structures *via* the bond cleavage of easily accessible scaffolds has recently attained growing attention from synthetic practitioners.[92] In this regard, Zheng[93] *et al.* in 2022 reported the Cu-catalyzed synthesis of pyridine-fused dihydrobenzofuran derivatives **167**. In their synthetic protocol, coumarins **163** and oximes **164** were reacted in the presence of CuBr (catalyst) along with Li$_2$CO$_3$ (used as an additive) to afford 2,3-dihydrobenzofurans **167** in low to high yields (16–85%) *via* the



R^1 = 5-Me, 5-Br, 5-CF_3 5-^{t}Bu 6-Cl, 7-F, H
R^2 = Me H
R^3 = Me, H, Ph
R^4 = Me, H, Ph
R^5 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_5, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-S-$CF_3C_6H_4$, 3-$OMeC_6H_4$, 3-FC_6H_4, 2-ClC_6H_4, naphthyl, furanyl, cyclohexyl
R^6 = Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 3-MeC_6H_4, 2-FC_6H_4, $C_3H_7(Ph)_2$, C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{17}, cyclopropyl, thiophenyl

Scheme 28 Synthesis of polycyclic 2-isoxazolyl-2,3-dihydrobenzofurans **146**.

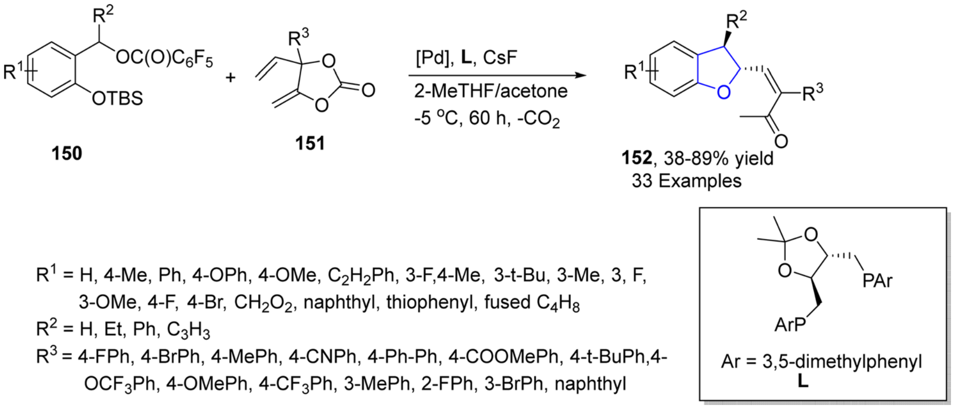


R = H, 3-Me, 4-Me, 2-Me, 3-OMe, 3-CF_3, 4-F, 4-Cl, 4-OMe, 4-CF_3, 4-piperidine, 3-isopentyl formate
R^1 = H, Me
R^2 = H, 2,2-$(Me)_2$-oxirane, 2-methylpentan-2-ol, 2-methylpent-2-ene
R^3 = H, ^{t}Bu, Ph, 4-$MeOC_6H_4$, 3-$CF_3C_6H_4$, C_2H_4OR, thiophene, 2-methylfuran, C_2H_4-phthalimide

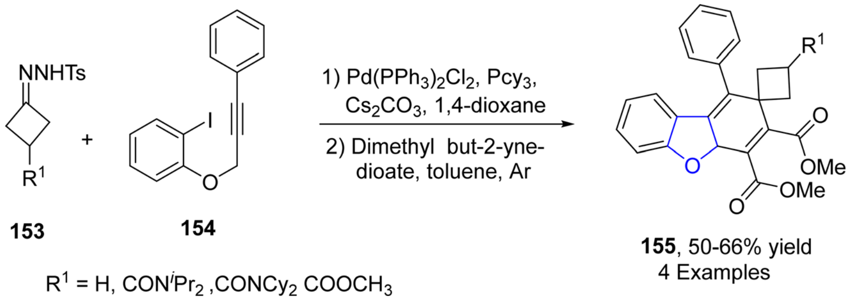
Scheme 29 Synthesis of 2,3-dihydrobenzofurans **148**.

destructive insertion of **164** into **163**. This synthetic methodology provides broad functional group tolerance. Cu-assisted oxime-Cu-iminyl radical was converted into α-carbon radical, which underwent radical addition to give intermediate **165**, followed by intramolecular addition to carbonyl group and oxidation to yield the desired products **167** (Scheme 34). The synthesized compounds were further transformed into a number of useful products to illustrate the proficiency of the developed synthetic route.

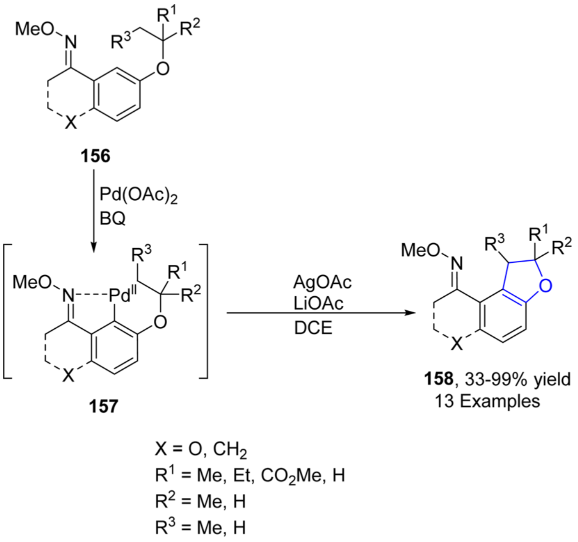
[3 + 2] cycloaddition reactions are pericyclic reactions, which involve the addition of a double bond system to a three-atom ring system. These cycloaddition reactions are amongst the most convenient synthetic protocols for the synthesis of five-membered heterocyclic ring compounds.[94] Considering this, in 2021, Jing[95] *et al.* described the synthesis of a range of enantioselective 2,3-dihydrobenzofurans **170** *via* the Cu/SPDO-catalyzed synthetic route. In their novel approach, quinone esters **168** and substituted styrenes **169** underwent [3 + 2] cycloaddition in the presence of SPDO-ligated $Cu(OTf)_2$ to furnish the desired dihydrobenzofuran moieties **170** in good to excellent yields (86–96%) with extraordinary enantioselectivities (86–99% ee) (Scheme 35). Natural products **171** and **172** were also synthesized by utilizing the mentioned methodological strategy (Fig. 8).



Scheme 30 Synthesis of 2,3-dihydrobenzofurans **152**.



Scheme 31 Synthesis of polycyclic 2,3-dihydrobenzofurans **155**.

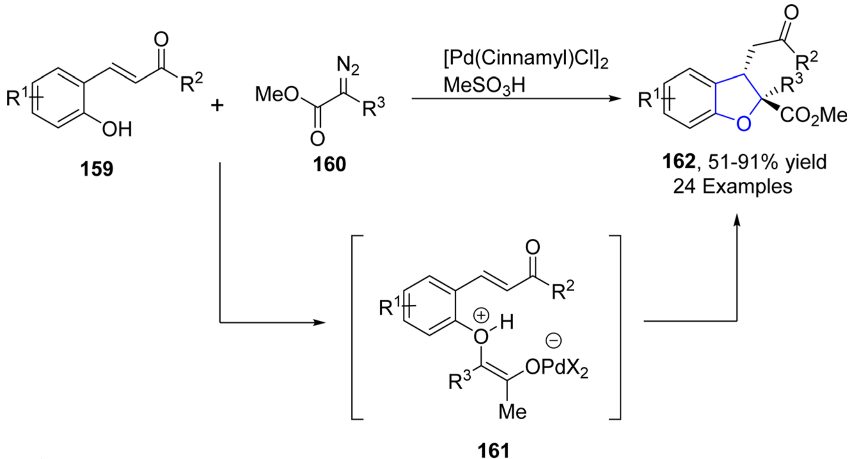


Scheme 32 Synthesis of fused cyclic dihydrobenzofurans **158**.

An enantioselective and diastereoselective pathway towards the synthesis of dihydrobenzofurans **163** was given by Zhu[96] *et al.* in 2023. They exploited copper(II)/SPDO complex (chiral spirocyclic pyrrolidine (oxazoline)) catalyst for carrying out asymmetric [3 + 2] cycloaddition reaction between 2,3-dihydrofuran **173** and quinone esters **168** utilizing copper triflate Cu(OTf)$_2$ and ligand **L** in toluene, wet tetrahydrofuran or mestylene solvent, to enable the asymmetric synthesis of benzofuran derivatives **175**. The reaction mechanism was suggested to move forward with the formation of intermediate **174**, on the coordination of substrates and catalyst. Intermediate **174** was then believed to undergo further transformations to furnish the synthesis of target molecules (Scheme 36). The developed synthetic route was further explored towards the synthesis of olefin variants-substituted dihydrobenzofurans (**A** & **B**) (Fig. 9) and naturally-occurring aflatoxins **96**, *i.e.*, (−)aflatoxin B$_2$ **96a** & (−)dihydroaflatoxin D$_2$ **96b** (Fig. 10).

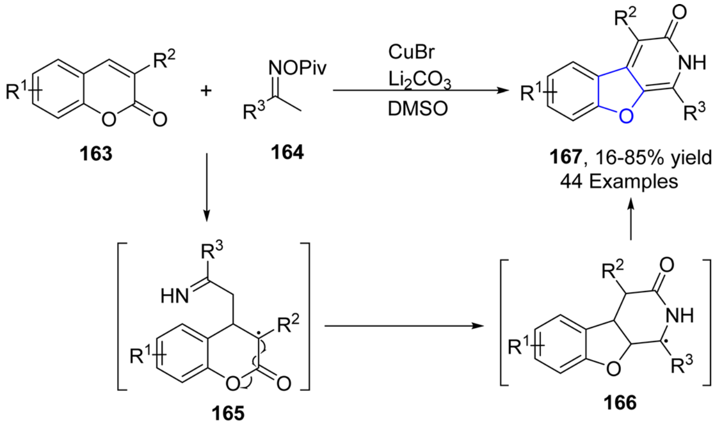
The five-membered O-containing compound, *i.e.*, 2-benzylidene-1-benzofuran-3-one, called aurone, showed a number of pharmacological activities like antidiabetic, antiviral and anticarcinogenic.[97] In 2021, Devi *et al.*[98] employed copper bromide-promoted synthesis of these 2-benzylidene-1-benzofuran-3-one derivatives **179**. For this purpose, they furnished chalcones **179** by treating aromatic aldehydes **177** with substituted acetophenone **176** utilizing montmorillonite K10 clay as a catalyst. The synthesized chalcones **179** were then subjected to copper bromide cyclization by employing dimethylformamide/water (7 : 3) as a solvent to attain substituted benzofuranone heterocycles **179** (Scheme 37).

In the same year, Mitsudo[99] *et al.* designed an efficient Cu-catalyzed protocol for the synthesis of dihydrofuran-fused thienoacenes **182** and **183** *via* C–O cyclization. In their novel methodology, 2-(benzo[*b*]thiophen-2-yl)phenols **180** and 2-(benzo[*b*]thiophen-3-yl)phenols **181** underwent the



R^1 = 5-Me, 5-OMe, 5-F, 5-Cl, 6-Me, H
R^2 = Me, C_6H_5, P-MeC_6H_4, *m*-MeOC_6H_4, Et, furanyl, thiophenyl
R^3 = C_6H_5, 4-MeC_6H_4, 4-^{t}BuC_6H_4, 4-PhC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 3-CF$_3$C$_6$H$_4$, 3,4-diClC_6H_3, 2-MeC_6H_5, 3,4-fused C_4H_4, COCH$_3$,

Scheme 33 Synthesis of 2,2,3-trisubstituted dihydrobenzofuran derivatives **162**.

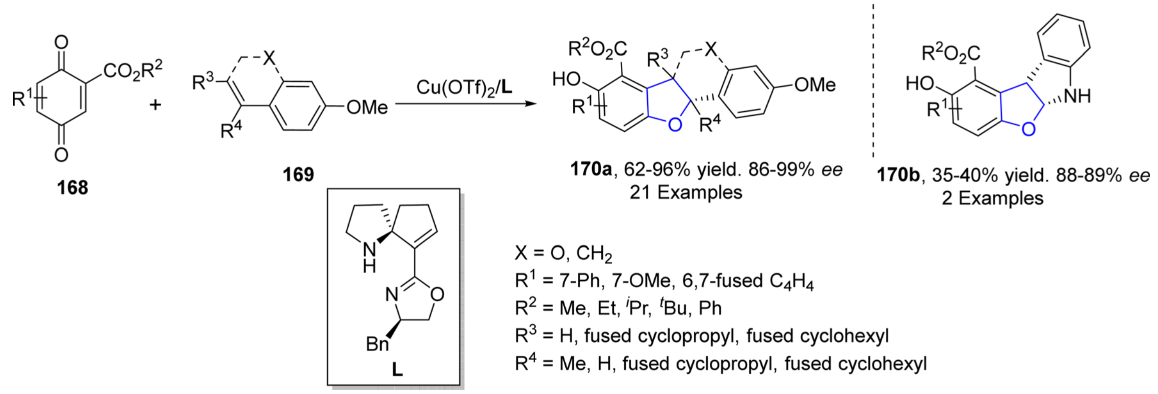


R^1 = 6-NEt, 6-OMeC_6H_4, 6-ClC_6H_4, 6-BrC_6H_4, 6-IC_6H_4, 5-CH$_3$, 5-FC_6H_4, 4,5-fusedC_4H_4, 4,5-diOMe, 5,7-^{t}Bu, 5,7-diCl, 5,7-diBr, 5,7-diI, 6-OC_9H_{17}
R^2 = CO$_2$Me, COPh, COC(C_3H_9), PO(EtO)$_2$, CO$_2$Et
R^3 = 4-^{t}BuC_6H_4, 4-MeC_6H_4, 4-OMeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-MeSC_6H_4, 4-CO$_2$MeC_6H_4, 4-CNC_6H_4, 4-CF$_3$C$_6$H$_4$, 3-ClC_6H_4, 3-CNC_6H_4, 2-MeC_6H_4, 3,4-diMeC_6H_4, 4-SO$_2$N(C_3H_7)$_2$C$_6$H$_4$, C_2H_2Ph, C_6H_5, benzodioxole, furanyl, thiophenyl, benzofuran, 1,Me-1*H*-indole, pyrridine, 1-Me-1*H*-pyrrole, 1-Me-1*H*-pyrazole, 3-(1-(3-(2-methoxyphenoxy)propyl)piperidin-4-yl)benzo[*d*]isoxazole

Scheme 34 Synthesis of 2,3-dihydrobenzofuran-fused pyridones **167**.

degenerative cyclization process to afford thieno[3,2-*b*]furans **182** (12–86%) or thieno[2,3-*b*]furans **183** (53–95%) respectively. Similarly, substrates **181** afforded heteroacenes **184** and **185** having π-expanded system *via* double C–O cyclization. The catalytic amount of Cu(OAc)$_2$, NaOAc (as base) and PhCOOH (as acid) were used to achieve the efficient yields of target molecules (Schemes 38 and 39).

Oxidative cross coupling is a strategy where two phenolic moieties are coupled together *via* an oxidative process to generate new C–C bonds.[100] Cu-catalyzed intermolecular oxidative cross coupling reactions have attracted much attention in organic synthesis to generate new dihydrobenzofuran units. In 2021, Dong[101] *et al.* developed a biomimetic, Cu-catalyzed synthesis of neolignane analogs comprising of 2,3-dihydrobenzofuran units **190.** In their novel methodology, substituted *para*-alkenyl phenols **188** were cross coupled with a number of electron rich phenols **20** to furnish 8-5′ neolignan correspondents **190** exclusively. Cu-assisted radical formation of phenols (**188, 20**) took place, which coupled to generate quinone methide intermediate

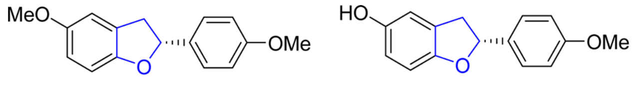


170a, 62-96% yield. 86-99% *ee*
21 Examples

170b, 35-40% yield. 88-89% *ee*
2 Examples

X = O, CH_2
R^1 = 7-Ph, 7-OMe, 6,7-fused C_4H_4
R^2 = Me, Et, ^{i}Pr, ^{t}Bu, Ph
R^3 = H, fused cyclopropyl, fused cyclohexyl
R^4 = Me, H, fused cyclopropyl, fused cyclohexyl

Scheme 35 Synthesis of 2-aryl-2,3-dihydrobenzofurans **170**.



171, corsifuran A **172**, corsifuran B

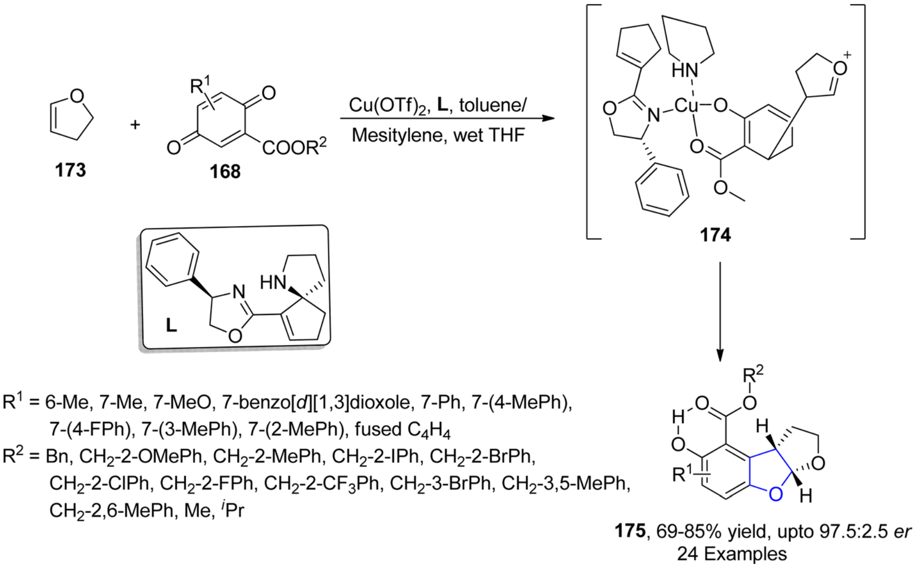
Fig. 8 Structure of asymmetric natural products **171** and **172**.

189, followed by the addition of –OH to **189** to afford the desired 2,3-dihydrobenzofuran skeletons **190** in excellent yields (24–95%) with notable diastereoselectivity values (>20 : 1 dr) (Scheme 40). Through the developed synthetic route, Licarin A **191** was also synthesized, which exhibits anti-inflammatory activity (Fig. 11).

2.4. Ni-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Nickel, which is also regarded as the "spirited horse" of TM catalysis, is a well-known metal catalyst used in organic synthesis.[102] Enantioselective Ni-catalyzed reductive Heck coupling of tethered alkenes has been utilized to furnish a range of benzene-fused heterocyclic rings bearing a quaternary stereogenic center.[103] In reference to this, Cerveri[104] *et al.* in 2021, synthesized a library of asymmetric 2,3-dihydrobenzofuran-3-ylacetic acids **193** *via* a tandem, enantioselective Ni-catalyzed Heck cross coupling reaction. In their novel methodology, CO_2 fixation took place when *o*-aryliodines **102** were cyclized in the presence of $[(\mathbf{L})_2Ni(H_2O)Cl]Cl$ (used as pre-catalyst), Zn (as reducing agent), tetrabutylammonium iodide (TBAI) and trimethylsilyl chloride (TMSCl) (as additives) to afford asymmetric dihydrobenzofuran derivatives **193**. Complex formation of compound **102** and NiL-precatalyst was carried out to form intermediate **192**, followed by subsequent Zn-mediated reduction and CO_2 insertion to afford the target compounds in moderate to high yields (47–69%) with up to 99% enantiomeric excess (Scheme 41).

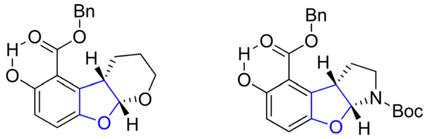
Pyrano-fused cyclic organic compounds are ubiquitously employed in medicinal chemistry owing to their unique



R^1 = 6-Me, 7-Me, 7-MeO, 7-benzo[*d*][1,3]dioxole, 7-Ph, 7-(4-MePh), 7-(4-FPh), 7-(3-MePh), 7-(2-MePh), fused C_4H_4
R^2 = Bn, CH_2-2-OMePh, CH_2-2-MePh, CH_2-2-IPh, CH_2-2-BrPh, CH_2-2-ClPh, CH_2-2-FPh, CH_2-2-CF_3Ph, CH_2-3-BrPh, CH_2-3,5-MePh, CH_2-2,6-MePh, Me, ^{i}Pr

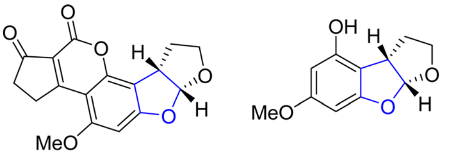
175, 69-85% yield, upto 97.5:2.5 *er*
24 Examples

Scheme 36 Synthesis of 2,3,3*a*,8*a*-tetrahydrofuro[2,3-*b*]benzofurans **175**.



A, 75%, 90:10 *er* **B**, 75%, 72.3:27.7 *er*

Fig. 9 Structures of olefin variant-substituted dihydrobenzofurans.



96a, (–)Aflatoxin B$_2$ **96b**, (–)Dihydroaflatoxin D$_2$

Fig. 10 Structures of naturally-occurring dihydrobenzofuran derivatives **96a** and **96b**.

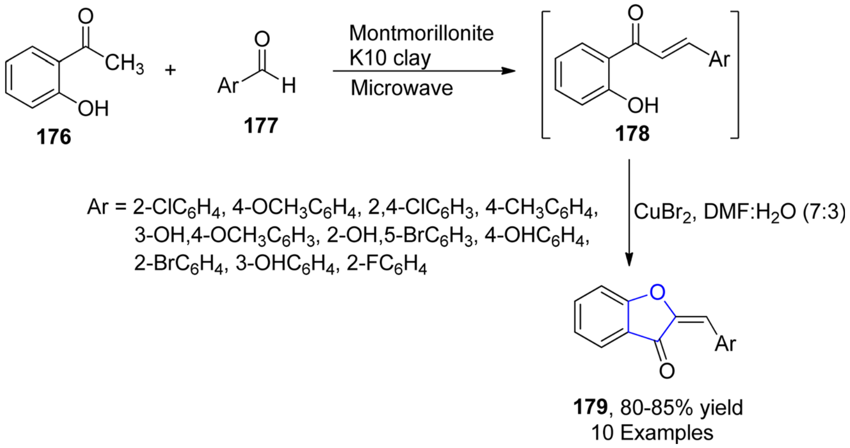
biologically active nature. There are mainly two types of these heterocycles based on the point of attachment of oxygen atom, *i.e.*, C3–C2 & C2–C1. In 2022, Bhardwaj[105] *et al.* reported a novel and efficient methodology by reacting enopyranoses **195** and iodine substituted phenols **194** under the action of nickel catalyst using cesium carbonate as a base in the presence of triphenylphosphine and dimethylformamide. This one-pot synthetic approach resulted in the straightforward synthesis of pyrano *cis*-fused dihydrobenzofurans **198** (47–75% yield). The reaction mechanism was proposed to proceed *via* the oxidative addition and carbometallation to form an intermediate **196**, followed by β-OAc elimination and allylic rearrangement to furnish the desired dihydrobenzofurans **197** (Scheme 42).

As a key component of several dicarbon-functionalization reactions, alkene aryl-acylation or aryl-carbamoylation facilitates the synthesis of structurally significant heterocycles comprising of carbonyl compounds.[106] In this respect, Wang[107] *et al.* in 2022 described a novel approach to afford dihydrobenzofuran derivatives **200** employing nickel-catalyzed aryl carbamoylation and aryl acylation of aryl iodide-joined alkenes **124**. Aryl iodide-joined alkenes **124** were subjected to treatment with aryl-substituted isocyanates **199** *via* Ni-catalyzed aryl carbamoylation to result in the efficient synthesis of substituted dihydrobenzofurans **200** (62–73%) (Scheme 43).

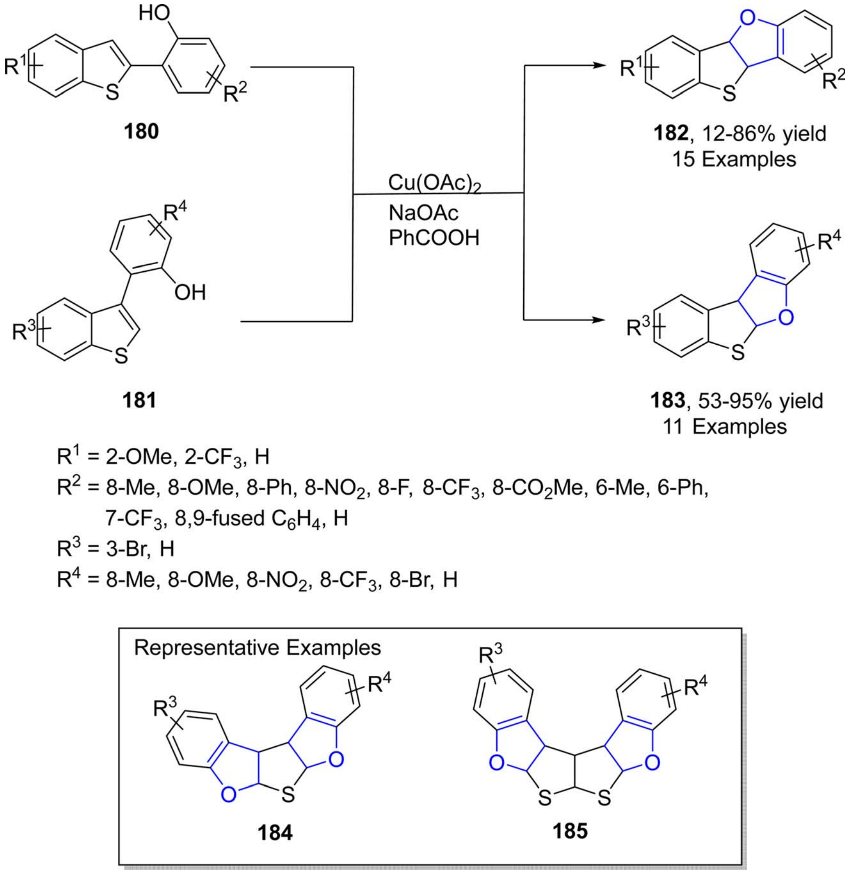
In 2021, Lin[108] *et al.* reported the Ni-catalyzed asymmetric synthesis of 2,3-dihydrobenzofuran derivatives **204** *via* the reductive aryl allylation process. In their synthetic approach, aryl iodides **102** were reacted with cyclic vinyl ethylene carbonates **203** to achieve cyclic products **204** in moderate to good yields (46–67%) with remarkable enantioselectivity values (>98% ee). Alkene-tethered aryl iodides **102** underwent oxidative addition with Ni catalyst to generate intermediate **201**, followed by olefinic migratory insertion to form cyclic intermediate **202**. Next, vinyl ethylene carbonates **203** were oxidatively added to the intermediate **202**, proceeded by reductive elimination to access the desired dihydrobenzofurans **204** (Scheme 44).

Geng[109] *et al.* in 2021 reported the Ni-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives **207** *via* carbonylative synthesis. In their novel methodology, *ortho*-substituted aryl iodides **124** reacted with alkyl halides **205** in the presence of Ni(acac)$_2$ (as a catalyst), 4,4′-di-*tert*-butyl-2,2′-bipyridyl (**L**) (as ligand), Mo(CO)$_6$ (as carbonylating agent) and Mn (as reductant) to furnish desired products **207** in low to excellent yield (38–87%). In the first step, activated Ni was oxidatively added to *ortho*-substituted aryl iodide **124**, followed by intramolecular addition to the carbonyl group and addition of alkyl halide **205** to generate intermediate **206.** The intermediate **206** was further subjected to reductive elimination to afford the 2,3-dihydrobenzofuran derivatives **207** (Scheme 45).

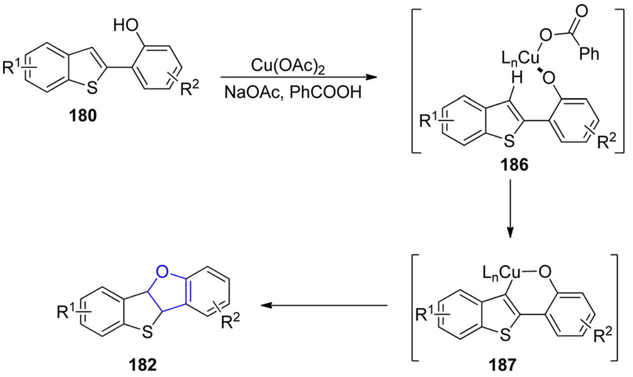
Electrification is an optimistic approach of replacing traditional energy-demanding chemical processes with greener substitutes and thus alleviating carbon emissions.[110] Utilizing this strategy, Déjardin[111] *et al.* in 2021, proposed an electroreductive, Ni-catalyzed synthesis of 2,3- dihydrobenzofuran derivatives **211** based on domino reaction. In this regard, intramolecular carbonickelation of propargylic aryl halides **208** was carried out, followed by the subsequent cyclization and nucleophilic addition of benzaldehydes **209** to furnish



Scheme 37 Synthesis of 2-benzylidene-1-benzofuran-3-ones **179**.



Scheme 38 Synthesis of furan-fused thienoacenes 182–185.



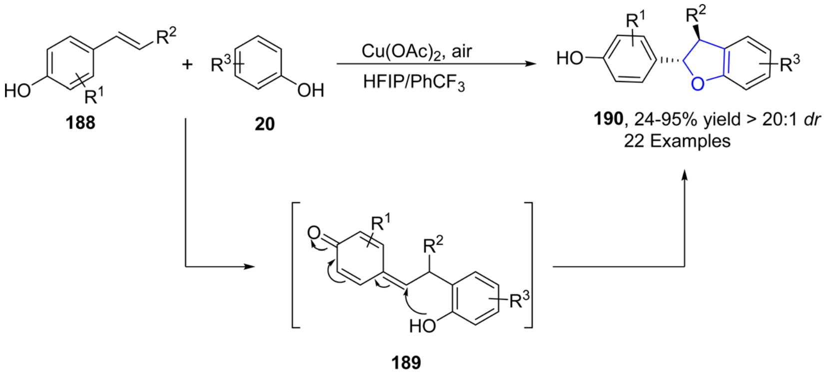
Scheme 39 Proposed mechanism for the synthesis of furan-fused thienoacenes 182.

substituted 2,3-dihydrobenzofuran **211** (11–90%). The reaction was highly stereo and regio-selective. Maximum yield (90%) was observed when the reaction proceeded at 80 °C in the presence of DMF (as a solvent) (Scheme 46).

2.5. Au-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

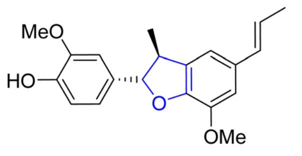
Au-containing catalytic systems are extensively studied in organic synthesis as they have exclusive low temperature oxidation activity. Au-catalyzed synthesis of heterocycles *via* [3 + 2] annulation portrays an appealing strategy as it offers complete regio- and stereo-control for introducing the functional groups. Utilizing this strategy, Liang[112] *et al.* in 2021 described the synthesis of polycyclic dihydrobenzofuran derivatives **215** *via* gold and Cu-catalyzed tandem reaction. In their synthetic approach, propargyl alcohols **212** were coupled with pyridylhomopropargylic alcohols **213** *via* a number of processes, *i.e.*, 5-*endo*–*dig* cyclization, Meyer–Schuster rearrangement and Friedel–Crafts-type reactions to furnish 2,3-dihydrobenzofurans **215** in low to high yields (14–81%) (Scheme 47).

In 2023, Morita[113] *et al.* carried out the efficient synthesis of dihydrobenzofurans by involving gold-based NHC catalyst (permethylated β-cyclodextrin-tagged *N*-heterocyclic carbene–gold catalyst) in water. They utilized the NHC catalyst due to the hydrophobic nature of β-CD,[114] which was expected to enhance the solubility of substrates with non-polar moieties in water. Moreover, NHC-based gold catalyst was assumed to activate the alcoholic functionality in benzylic alcohols **217** and carbonyl functionality in *p*-quinones **216** to facilitate the synthesis of dihydrobenzofurans **197**. Substituted *p*-quinones **216** were treated with isoeugenols *via* [3 + 2] cycloaddition reaction in the presence of β-CD–NHC–AuCl catalyst, utilizing $AgNTf_2$ (as an additive) in the excess of water to result in the efficient asymmetric synthesis of target molecules **218** in 31–81% yield (Scheme 48).



R^1 = 3-OMe, 3,5-diOMe, 2-Cl, 3-Cl, 3-Br, 2-Br-6-OMe, $N(C_2H_6)$, H
R^2 = Me, C_2H_5, 3,5-diOMeC_6H_3, H
R^3 = NMe_2, NHC_6H_5, NHMe, OMe, $COCH_3$, C_3H_5, $NHCH_2C_6H_5$, morpholine, furan-2-yl-methanamine, (piperazin-1-yl)ethanone, cyclopentanamine

Scheme 40 Synthesis of neolignan analogs comprising of 2,3-dihydrobenzofuran **190**.

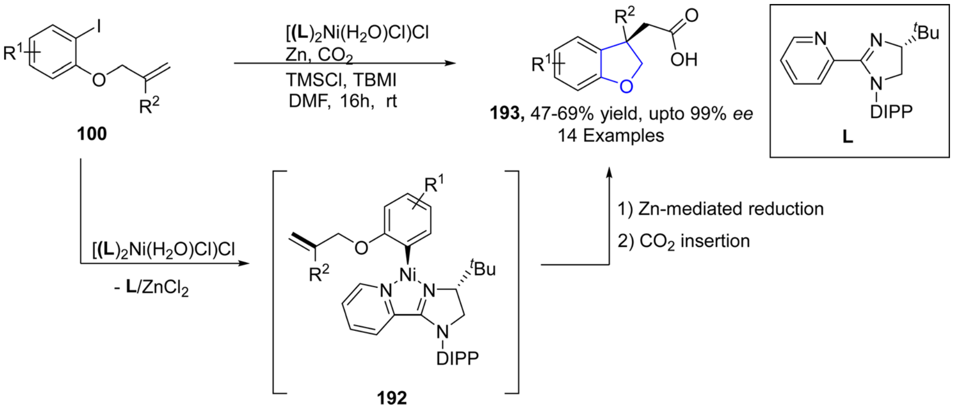


191, Licarin A, 60% yield, >20:1 *dr* (anti inflammatory)

Fig. 11 Structure of licarin A **191**.

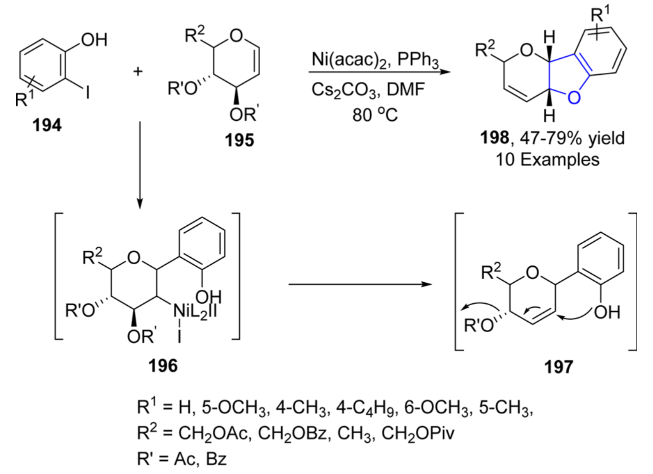
Wang[115] *et al.* in 2021 accomplished the gold-catalyzed [2 + 3] cycloaddition of phenols **20** and substituted-1,3-enynes **219** to furnish dihydrobenzofuran scaffolds **221** in low to high yields (25–81%). In their synthetic methodology, the *ortho*-selectivity of phenols **20** was attained for the first time *via* electrophilic aromatic substitution employing **219** as an α-oxo vinyl gold carbenoid analogue. Catalytic amounts of ^{t}BuXPhosAuCl (phosphine ligated aurum catalyst) and 2,6-dichloropyridine *N*-oxide **222** (as an additive) were utilized in dichloroethane to achieve the desired products **221.** Gold and ligand **222** assisted 1,3-enynes **219** underwent concerted S_N2 reaction and proto-deauration upon the addition of substituted phenols **20** to generate intermediate **220.** The intermediate **220** was converted to the final product **221** *via* oxa-Michael addition (Scheme 49).

Du[116] *et al.* in 2023 disclosed a gold-catalyzed, one-pot construction of benzofuran-3(2*H*)-one skeletons **226** using the phenomenon of cycloisomerization of alkynyl phenols **223.** In their novel methodology, *o*-alkynyl phenols **223** were reacted with substituted alcohols **224** in the presence of Ph_3PAuCl (catalyst), Selectfluor (as an oxidant) and TfOH (as an additive) to afford benzofuranones **226** in moderate to good yields (22–76%). *o*-Alkynyl phenols **223** were activated and oxidatively added to its phenolic part to form a cyclic intermediate, which was oxidized by Selectfluor. In the next step, reductive elimination took place, followed by the nucleophilic substitution



R^1 = 5-^{t}Bu-7Me, 5-C_2H_4-Ph, 5-Me, 5-^{t}Bu, 5-F, 5-^{i}Pr-6-Me, 5-$C_2H_4CO_2$Et, 5-$C_2H_4CO_2{}^n$Pr, 5-$C_2H_4CO_2$CH-(Ph)OMe, H
R^2 = Me, Bn, C_8H_{17}, OMe.

Scheme 41 Synthesis of 2,3-dihydrobenzofuran-3-ylacetic acids **193**.



Scheme 42 Synthesis of pyrano *cis*-fused dihydrobenzofurans **198**.

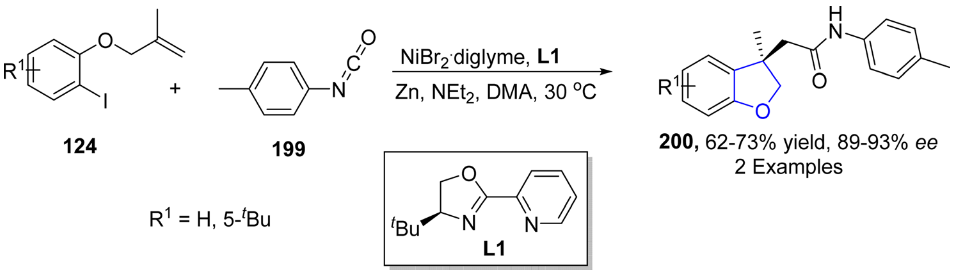
reaction to generate intermediate **225**. This intermediate then underwent ketal hydrolysis to furnish the final products **226** (Scheme 50).

2.6. Ru-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

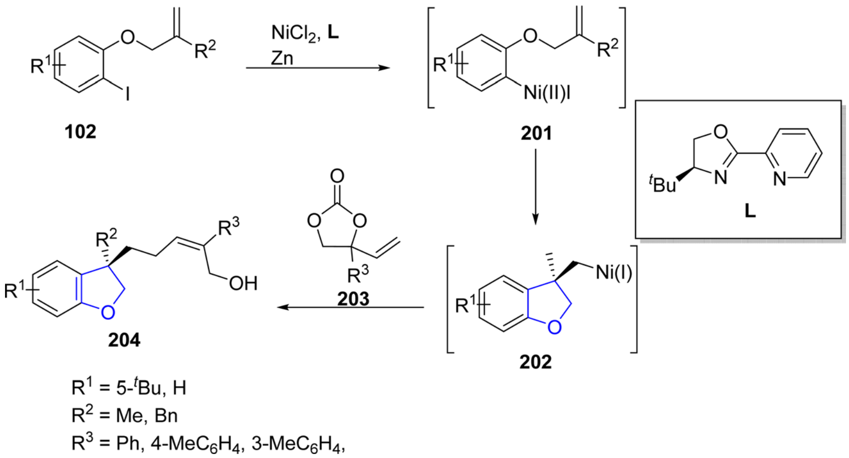
Ruthenium, though being the rarest earth metal, is widely used as a catalyst in organic transformations. The Ru-catalyzed synthesis of dihydrobenzofuran derivatives *via* C–C and C–H bond functionalization has gained tremendous attention in organic synthesis. Directing groups accompanied enantioselective functionalization of C–H bonds promoted by TM catalysts has gained significant utility in several organic transformations. In 2023, Sau[117] *et al.* carried out the synthesis of chiral dihydrobenzofuran derivatives **228** *via* ruthenium-catalyzed C–H functionalization of 3-(allyloxy)benzamides **227** in the presence of AgSbF$_6$, using copper acetate (as an additive) in 1,2-dichloroethane. The synthesized optically active dihydrobenzofurans were then subjected to treatment with substituted alkynes **36** in acetic acid to afford dihydrobenzofuran-fused isoquinolinones **228** in high enantiomeric excess (up to 97 : 3 er) along with a side product **229** (Scheme 51).

Similarly, Pannilawithana *et al.*[118] utilized ruthenium catalyst-mediated synthesis of dihydrobenzofuran heterocycles by treating varied phenols **20** with substituted aldehydes **230**. The coupling reaction was efficiently carried out in the presence of carbon monoxide and dichloroethane as CO addition greatly enhanced the yield of benzofuran derivatives **231** (64–93%) in comparison to alkylation products **232** (side product) (Scheme 52).

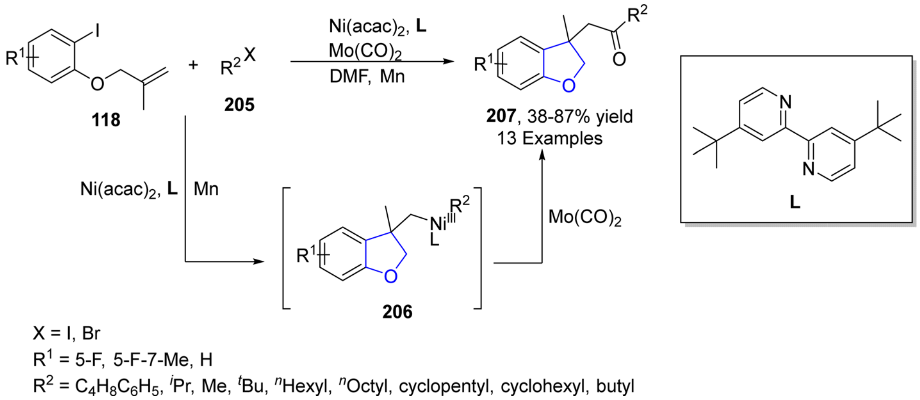
Utilizing the annulation reaction strategy, another ruthenium-catalyzed approach for the facile synthesis of dihydrobenzofurans was demonstrated by Phukon[119] *et al.* in 2023.



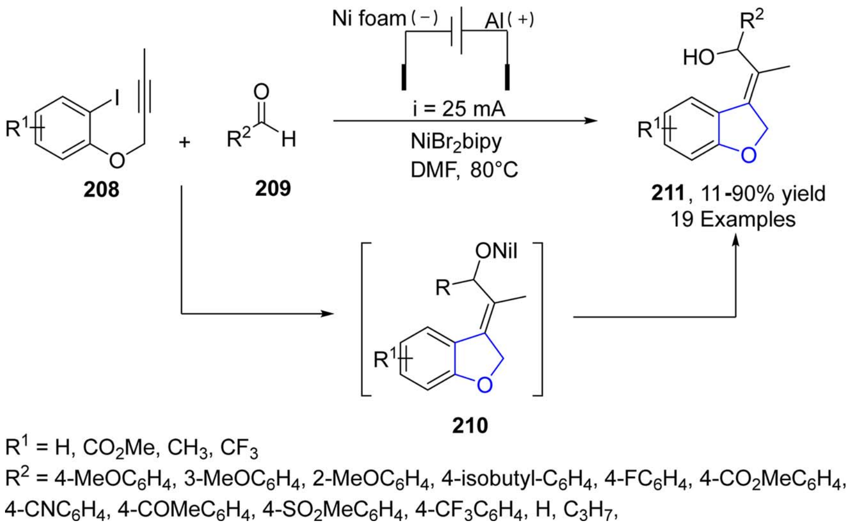
Scheme 43 Synthesis of substituted dihydrobenzofurans **200**.



Scheme 44 Synthesis of 2,3-dihydrobenzofuran **204**.



Scheme 45 Synthesis 2,3-dihydrobenzofuran derivatives **207**.



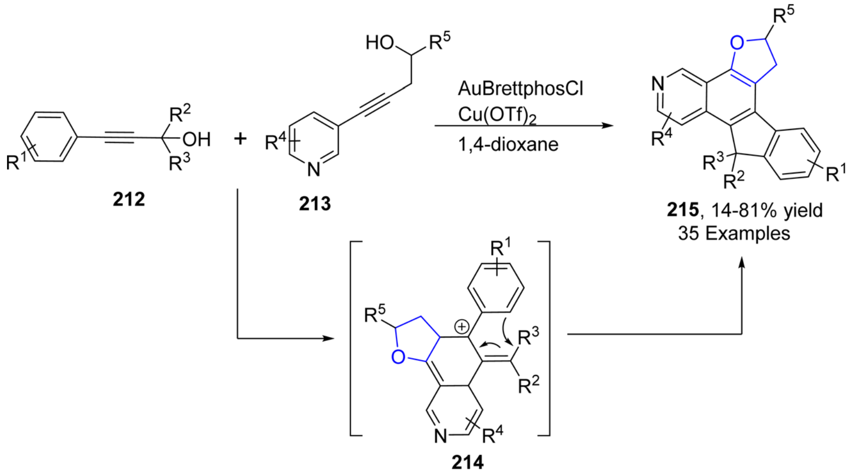
Scheme 46 Synthesis of 2,3-dihydrobenzofuran derivatives **211**.

In the developed synthetic methodology, substituted naphthols **234** were made to react with substituted sulfoxonium ylides **233** *via* the cyclization reaction, which involved the employment of 1,4-dioxane (as a source of $-CH_2$) and copper acetate to synthesize dihydronaphthofurans **235** in 51–68% yield (Scheme 53).

In 2021, Yuan[120] *et al.* successfully designed a multicomponent, photoredox catalytic protocol that was applied for the construction of dihydrobenzofuran ring systems **240**. For this purpose, 2-vinyl phenols **44**, *N*-alkoxypyridinium salts **236** and sulfur ylides **237** were coupled in the presence of $Ru(bpy)_3Cl_2\cdot 6H_2O$ as an efficient photocatalyst along with CuI/ligand (**L**) in DABCO. Ru catalyst facilitated the formation of sulfonium ylide and alkoxy radical that got transformed into benzylic radical intermediate **238** by reacting with *in situ* formed 2-vinylphenolate. Benzylic intermediate **238** further interacted with sulfonium ylides **237** to form **239**, followed by nucleophilic substitution reaction to furnish the desired cyclized products **240** in low to good yields (26–74%) (Scheme 54).

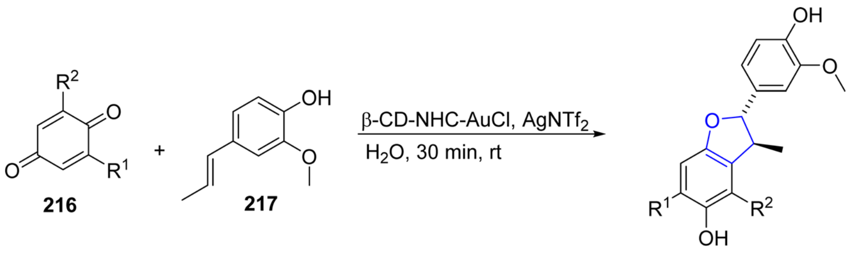
2.7. Ir-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Iridium is the most corrosion resistance metal, which displays variable oxidation states and is utilized as a good catalyst in several organic transformations. Cross-dehydrogenative coupling (CDC) is an efficient approach to afford various organic frameworks by involving the formation of C–C bond *via* two inequal C–H bonds. This synthetic transformation is highly ecofriendly and requires a short duration.[121] The synthesis of several sophisticated heterocycles can be achieved by the intramolecular cross-dehydrogenative coupling (first given by Fagnou and Liégault), which involves the fusion of alkyl groups to the aromatic ring. Kusaka[122] *et al.* in 2022 presented the enantioselective synthesis of dihydrobenzofurans **242** exploiting intramolecular CDC C(sp^2)–H/C(sp^3)–H. They carried out this approach on silyl-based aryl ethers **241** using iridium-based (*S*)-DTBM-SEGPHOS as a catalyst and *tert*-butyl ethylene (TBE) as a hydrogen collector involving *p*-xylene as a solvent to furnish enantioenriched dihydrobenzofuran derivatives **243** in 53–86% yield range with up to 99% ee. The reaction was proposed to



R^1 = 10-OMe, 10-F, 11-OMe,12-OMe, 10-OMe, 10-Me, 12-Me, 10-Et, H, 10,12-diMe, CF$_{3,}$ 10-Ph, 10-COOMe, 10-NO$_2$, 10-F, 10-Cl, 10-Br, thiophenyl
R^2 = Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-OMeC$_6$H$_4$,
R^3 = Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-Ph-C$_6$H$_4$,
R^4 = 6-Me, 6-Cl, 6-F, H
R^5 = Me, diMe, H,

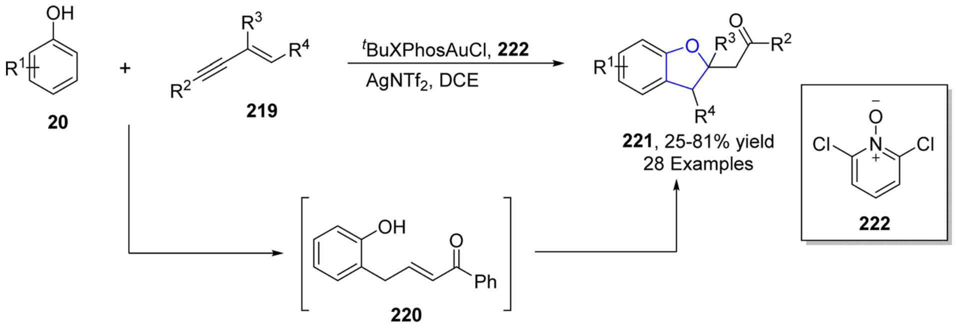
Scheme 47 Synthesis of polycyclic dihydrobenzofuran derivatives **215**.



R = H, OMe, Me,
R^2 = H, Me

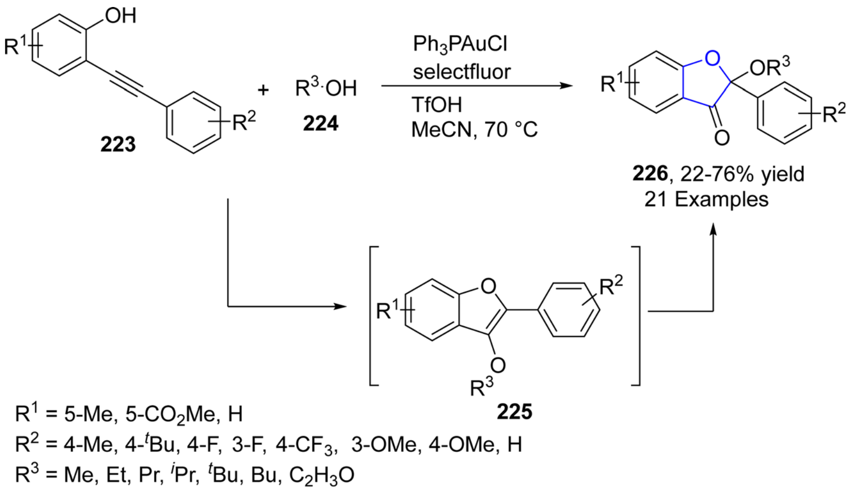
218, 31-81% yield
trans/cis = 92:8-99:1
3 Examples

Scheme 48 Synthesis of 2,3-disubstituted dihydrobenzofurans **218**.

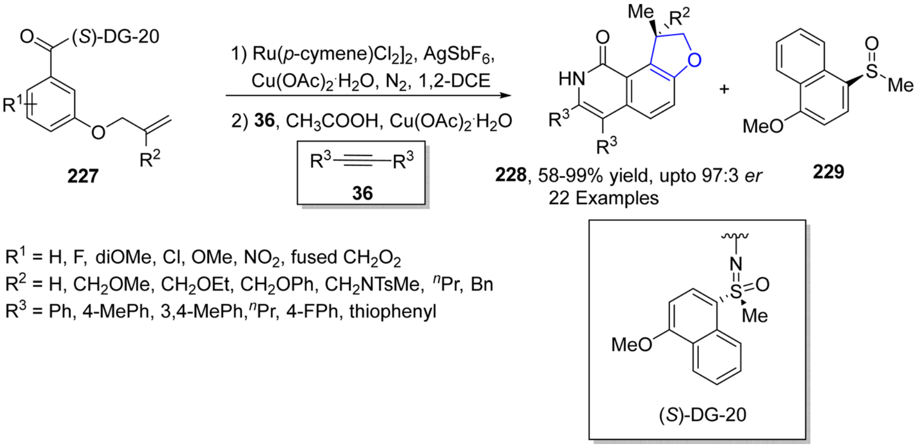


R^1 = 2-CH$_3$, 2,3-diCH$_3$, 6,7-fused C$_5$H$_6$, 6,7-fused C$_6$H$_8$, 6,7-fused C$_6$H$_4$ 4,5-fused C$_6$H$_4$, 2,4-diCH$_3$, 3,4,5-triCH$_3$, 4-CH$_3$,4-^{t}Bu, 4-OCH$_3$
R^2 = 4-MeC$_6$H$_4$, 4-^{n}BuC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-C$_6$H$_5$, 3,4-fused C$_6$H$_4$, C$_6$H$_5$, 1,2dihydrocyclohexenyl
R^3 = R^4 = H, Me

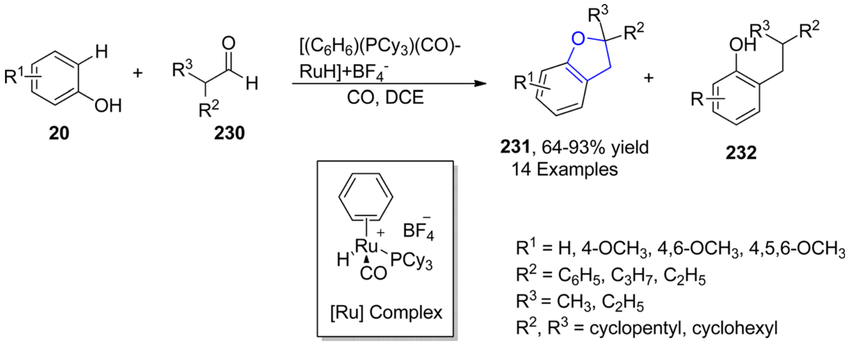
Scheme 49 Synthesis of 2,3-dihydrobenzofuran derivatives **221**.



Scheme 50 Synthesis of benzofuran-3(2*H*)-ones **226**.



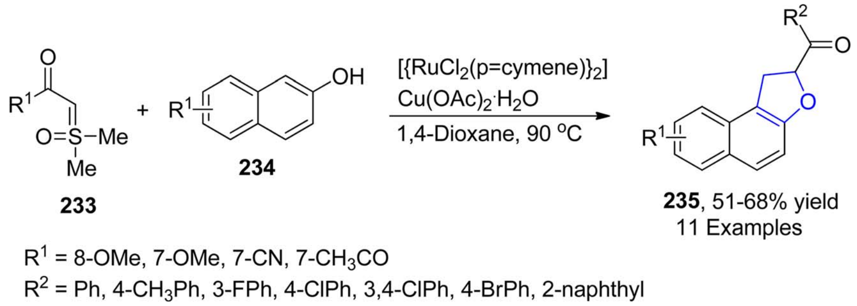
Scheme 51 Synthesis of dihydrobenzofuran-fused isoquinolinones **228**.



Scheme 52 Synthesis of dihydrobenzofuran heterocycles **231**.

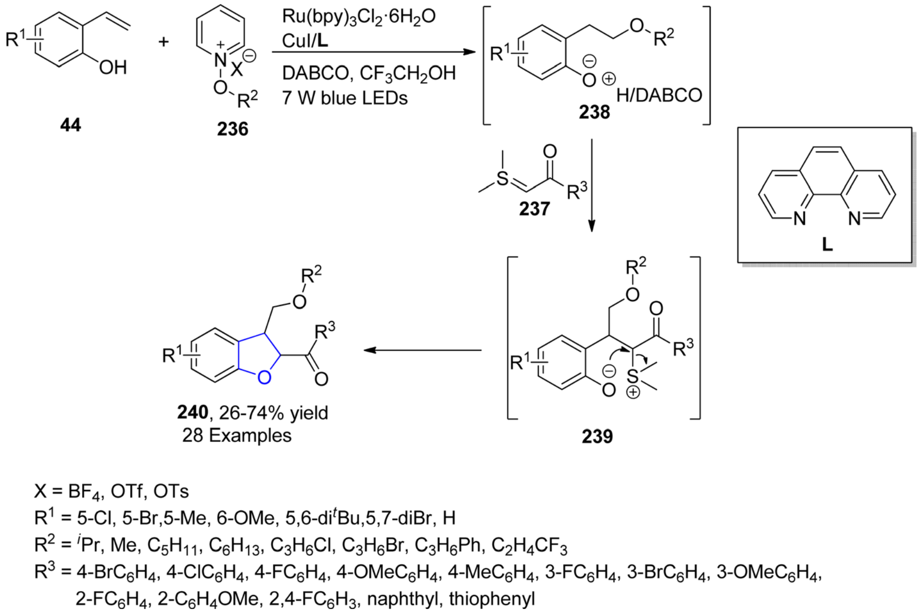
proceed *via* oxidative addition of **241**, followed by the removal of hydrogen and ligand exchange, leading towards the synthesis of aryliridium intermediate **242**. The intermediate **242** then underwent cyclization and reductive elimination to give dihydrobenzofurans **243** in high enantiomeric excess (up to 99% ee) (Scheme 55).

TM-catalyzed intramolecular straightforward addition of aromatic C–H bonds to olefinic bonds, named hydroarylation, has presented facile pathways towards the cyclic compounds with efficient atom-economy.[123] Utilizing the intramolecular hydroarylation strategy, in 2021, Sakamoto and Nishimura[124] described the Ir-catalyzed, enantioselective synthesis of 2,3-



R^1 = 8-OMe, 7-OMe, 7-CN, 7-CH_3CO
R^2 = Ph, 4-CH_3Ph, 3-FPh, 4-ClPh, 3,4-ClPh, 4-BrPh, 2-naphthyl

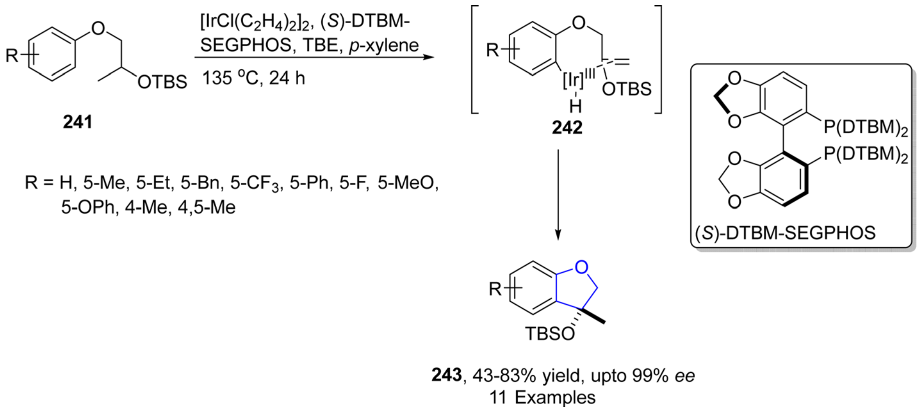
Scheme 53 Synthesis of dihydronaphthofurans **235**.



X = BF_4, OTf, OTs
R^1 = 5-Cl, 5-Br,5-Me, 6-OMe, 5,6-di^{t}Bu,5,7-diBr, H
R^2 = ^{i}Pr, Me, C_5H_{11}, C_6H_{13}, C_3H_6Cl, C_3H_6Br, C_3H_6Ph, $C_2H_4CF_3$
R^3 = 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$OMeC_6H_4$, 4-MeC_6H_4, 3-FC_6H_4, 3-BrC_6H_4, 3-$OMeC_6H_4$, 2-FC_6H_4, 2-C_6H_4OMe, 2,4-FC_6H_3, naphthyl, thiophenyl

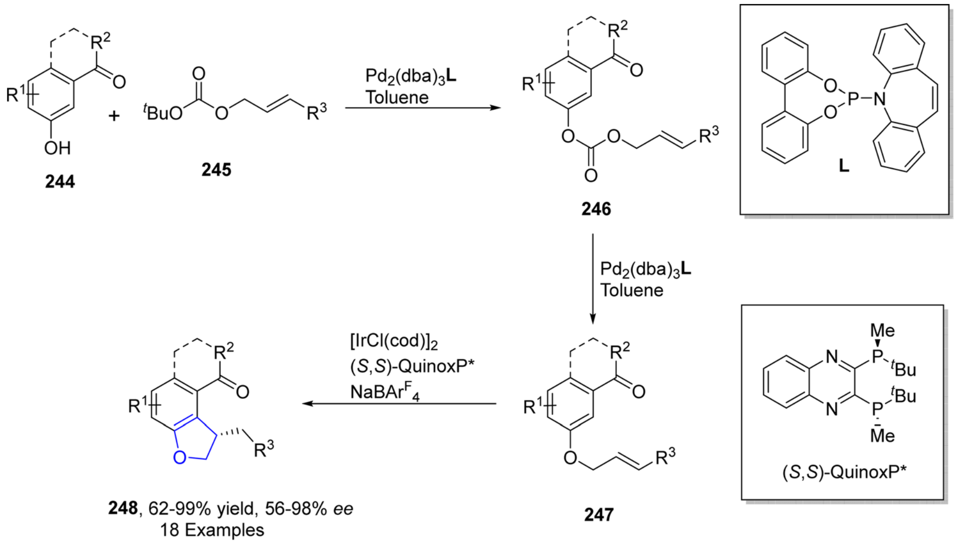
Scheme 54 Synthesis of dihydrobenzofuran derivatives **240**.

dihydrobenzofuran derivatives **248** *via* C–H activated intramolecular hydroarylation. In their novel methodology, they used one-pot protocol to attain desired cyclic products **248** in good to excellent yields (62–99%). Pd-catalyst was used to generate *m*-cinnamyloxyphenyl ketones **247** from allyl carbonate **246**, followed by the Ir-catalyzed protocol to afford 2,3-dihydrobenzofuran compounds **248**. A bisphosphine ligand, *i.e.*, (*S*,*S*)-QuinoxP*, was used to attain higher enantioselectivities (>98% ee) (Scheme 56).



R = H, 5-Me, 5-Et, 5-Bn, 5-CF_3, 5-Ph, 5-F, 5-MeO, 5-OPh, 4-Me, 4,5-Me

Scheme 55 Synthesis of dihydrobenzofuran derivatives **243**.

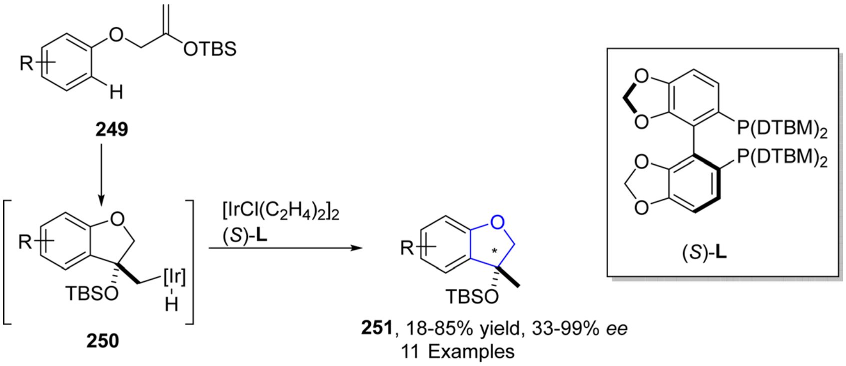


R^1 = H, 6-OMe

R^2 = 4-$NMe_2C_6H_4$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$, 3,5-$Me_2C_6H_3$, ^{i}Pr, ^{n}Bu, Me, cyclohexanone

R^3 = Ph, 4-$OMeC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 3-MeC_6H_4, 2-$OMeC_6H_4$, C_5H_{11}, furanyl

Scheme 56 Synthesis of 2,3-dihydrobenzofuran derivatives **248**.



R = 5-Me, 5-OMe, 5-CF_3, 5-Ph, 5-$SiMe_3$, 5-Cl, 5-F, 6-Me, 6-OMe, 7-Me

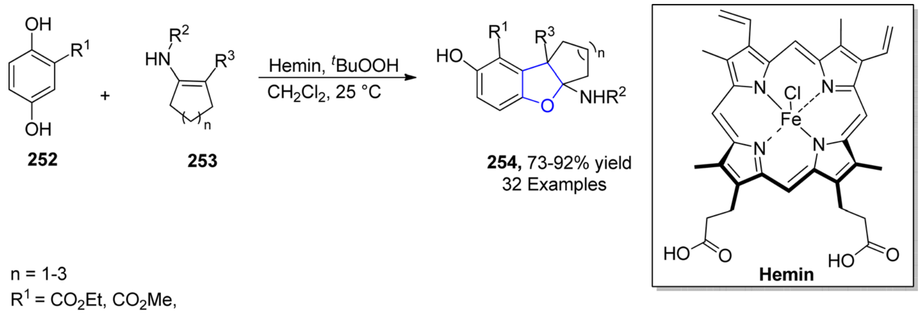
Scheme 57 Synthesis of 2,3-dihydrobenzofuran **251**.

In 2021, Ohmura[125] *et al.* reported the synthesis of enantioselective 2,3-dihydrobenzofuran scaffolds **251** *via* iridium-catalyzed intramolecular hydroarylation. In their novel methodology, *tert*-butyldimethylsilyloxy-substituted aryl ethers **249** acted as starting materials that were transformed into dihydrobenzofurans **251** (featuring a stereogenic carbon at C3 position) in low to excellent yields (18–85%) with significant enantioselectivity values (33–99%) (Scheme 57).

2.8. Fe-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Being inexpensive and earth friendly, iron (Fe) and its salts have become highly enticing. These parameters led the researchers to increase focus towards the iron-based catalysis for temperate and green reactions.[126] Bashir[127] *et al.* in 2023 proposed a facile method for the synthesis of 2,3-dihydrobenzofurans **254** *via* [3 + 2] cycloaddition. In this regard, substituted hydroquinones **252** were made to react with *N*-arylated cyclic enamines **253** in the presence of a biomimetic catalyst, *i.e.*, hemin (an iron embedded porphyrin) with an oxidant partner, *i.e.*, ^{t}BuOOH. Low to high yields (27–91%) were obtained by employing different catalytic loadings, CH_2Cl_2 (solvent) at room temperature for 10 hours (Scheme 58). The synthesized compounds were evaluated for their anti-cancerous potential against MCF-7 cancer cells, among which the compound with 2-propyne *N*-substitution exhibited potent IC_{50} value = 27.73 μM.

In 2021, Zhang[128] *et al.* reported the iron(III)-mediated, free radical-catalyzed cascade protocol for the synthesis of naphthodihydrofurans **258**. In their novel approach,



252 + **253** → **254**, 73-92% yield
32 Examples

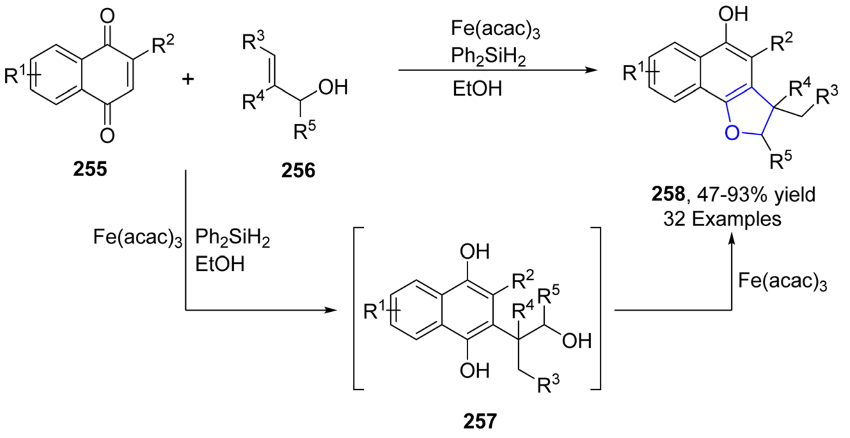
n = 1-3
R^1 = CO_2Et, CO_2Me,
R^2 = 4-F-3-IC_6H_3, 4-F-3-MeC_6H_3, 2,4,6-tri$CH_3C_6H_3$, cyclohexyl, cyclopropyl, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-MeOC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 3-BrC_6H_4, 3-IC_6H_4, 2,6-diC_2H_5-PhC_6H_4, naphthyl, Ph, CH_2Ph, C_2H_4-4-MeC_6H_4, C_2H_4-OTBS, C_2H_5, C_4H_9, 2-C_4H_8, C_3H_3, C_3H_5.
R^3 = CO_2Et, CO_2Me

Scheme 58 Synthesis of 2,3-dihydrobenzofuran **254**.

naphthoquinones **255** were reacted with allyl alcohols **256** in the presence of $Fe(acac)_3$ and Ph_2SiH_2 (used as reductant) in EtOH to access naphthodihydrofurans **258** in moderate to excellent yields (47–93%). Alkyl radical formed from **256** and naphthoquinones **255** underwent Michael addition and single electron transfer process to form intermediate **257**, which was dehydrated and cyclized to yield desired products **258** (Scheme 59). The gram scale synthesis of **258** was performed to scale up the reaction and structurally important 3,3-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-diones were also generated from the synthesized naphthodihydrofurans **258**.

2.9. Ag-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Ag-catalyzed [3 + 2] annulation reactions are the most convenient synthetic strategies for the synthesis of five-membered heterocyclic ring compounds.[94] In this context, in 2023, Guo[129] *et al.* executed visible-light promoted, additive-free synthesis of dihydrobenzofurans **261** and **262**. They treated substituted phenols **20** with styrenes **259** and *N*-acylindoles **260** in the presence of nanoparticles-based silver phosphate (Ag_3PO_4) in dichloromethane or HFIP solvent, to accomplish the synthesis of dihydrobenzofurans and indolines constituting dihydrobenzofurans **261** and **262**, respectively. This visible light-induced synthetic route proved to be high yielding and efficient due to the recyclable nature of nanoparticles-supported silver phosphate catalyst. On the catalytic surface, the stabilized radical cations of both substrates underwent [3 + 2] cross coupling reaction to yield the target molecules. Initially, the radical formation of substrates took place, which resulted in the formation of the radical cation intermediate. This intermediate radially

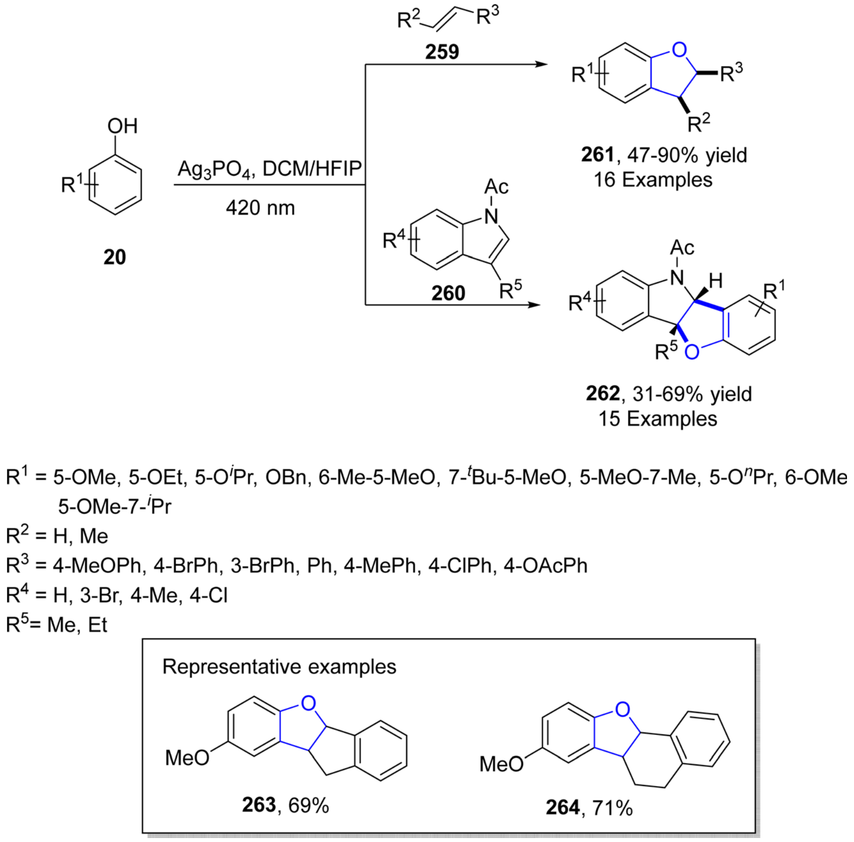


255 + **256** → **258**, 47-93% yield
32 Examples

257

R^1 = 7,8-Br, H
R^2 = C_6H_5, 4-FC_6H_4, 4-OMeC_6H_4, Indole, 1-Me-1*H*-indole, 4-Br-1-Me-1*H*-indole, 4-Br-1-Me-1*H*-indole, 5-Br-1-Me-1*H*-indole, 6-OMe-1-Me-1*H*-indole, 1,7-Me-1*H*-indole, 6-F-1-Me-1*H*-indole, 6-Cl-1-Me-1*H*-indole
R^3 = Me, H
R^4 = Me, H, cyclohexyl
R^5 = 4-MeC_6H_4, 4-OMeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, Me, H

Scheme 59 Synthesis of naphthodihydrofurans **258**.



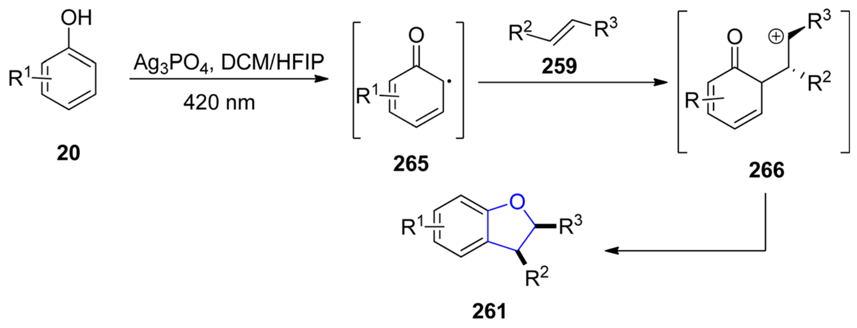
Scheme 60 Synthesis of dihydrobenzofurans **261** and **264**.

eliminates a proton to furnish the desired 2,3-dihydrobenzofuran derivatives **261** and **262** (Scheme 60). The proposed mechanism of the reaction was supposed to be initiated with the formation of radical species **265**, which cross coupled with the radical cation of **259** to form an intermediate **266**. Finally, this intermediate led to the synthesis of target molecules **261** upon deprotonation and cyclization (Scheme 61).

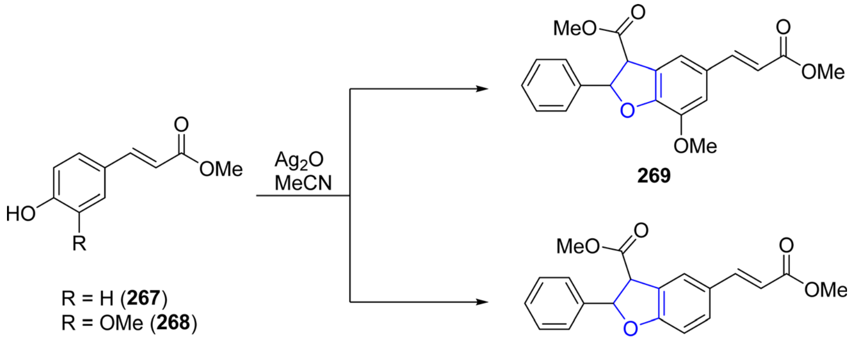
In 2021, Dias and coworkers[130] also optimized a silver-catalyzed method for the synthesis of 2,3-dihydrobenzofuran neolignans **269** and **270** *via* oxidative coupling strategy. In their synthetic approach, methyl *p*-coumarates **267** and methyl ferulates **268** were transformed into **269** and **270**, respectively, in the presence of Ag_2O (used as catalyst) and azobisisobutyronitrile (as radical inhibitor) in acetonitrile. These conditions furnished significant stability between conversion and selectivity (with 45% conversion and more than 71% selectivity) of dihydrobenzofurans **269** and **270** (Scheme 62).

2.10. Pt-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Platinum (Pt) catalysts depict astounding capacity as a carbon monoxide (CO) oxidation catalyst in the catalytic converter on account of their exceptional stability and tailoring adaptability. They are also widely utilized as electrodes in electrosynthesis. Electrosynthesis has gained significant weightage in organic



Scheme 61 Proposed mechanism for the synthesis of dihydrobenzofurans **261**.



Scheme 62 Synthesis of 2,3-dihydrobenzofuran neolignans **269** and **270**.

synthesis owing to the green applicability of electrons in proceeding redox reactions. However, its industrial usage is limited due to the bulk waste generation as a result of using concentrated supporting electrolytes.[131] Regarding to this, Okamoto[132] *et al.* in 2023 reported the synthesis of dihydrobenzofuran derivatives **271** by employing an electrochemical approach utilizing ultra-low electrolyte concentration (0.001–0.01 M). For the first time, they treated alkenes **21** and phenols **20** *via* electrochemically-induced [3 + 2] cycloaddition in the presence of flow microreactor using HFIP as the solvent. Bu_4NPF_6 (tetrabutylammonium hexafluorophosphate) was added with dichloromethane and acetic acid to be used as an electrolyte in the chemical reaction. Their synthetic route was highly productive and environment friendly owing to the complete elimination of waste production, thereby giving substituted dihydrobenzofurans **271** in 21–91% yield. Phenoxonium cations of **20** were formed anodically, which were further reacted with **21** to afford 2,3-dihydrobenzofuran derivatives **271** (Scheme 63).

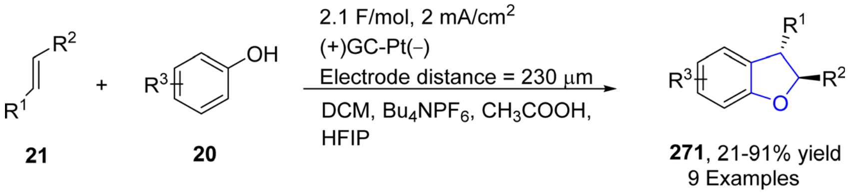
In 2023, Guan's[133] group reported another catalyst free, environmentally benign electrochemical synthesis of dihydrobenzofurans **275**. They treated substituted aminophenols **272** with diverse variety of olefins *via* an electrochemically-mediated approach in the presence of $^{n}Bu_4NBF_4$ in acetonitrile solvent to carry out the synthesis of target molecules in effective yields (33–99%). The developed route was found to be highly economical as it avoids the use of any catalyst, oxidizing agent and additive. The proposed mechanism of this reaction involved the anodic oxidation of substituted aminophenols **272** *via* single electron transfer, followed by an addition reaction with alkenes **273** to form intermediate **274**. The resulting intermediate was then supposed to form the carbocation, which ultimately afforded dihydrobenzofurans **275**, followed by intramolecular cyclization (Scheme 64).

2.11. V-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Vanadium (V), being a transition metal, has the capability to change its oxidation state and is used as an efficient catalyst for many reaction systems. Utilizing the V-catalyzed synthetic protocol, Wang[134] *et al.* in 2023, treated the substituted aryl acetates **277** and dihydroxy substituted naphthoic acid esters **276** *via* the [3 + 2] cascade reaction to afford dihydrobenzofuran derivatives **279** in 20–88% yield. The reaction was executed in the presence of catalytic isothiourea and vanadium oxide acetate utilizing hydrogen peroxide, *n*-Bu_4NHSO_4 and $B(OMe)_3$ in 1,4-dioxane. The postulated mechanism involved the formation of C1-ammonium enolate and removal of proton, followed by Michael addition and lactonization to furnish dihydrobenzofuran derivatives **279** (Scheme 65).

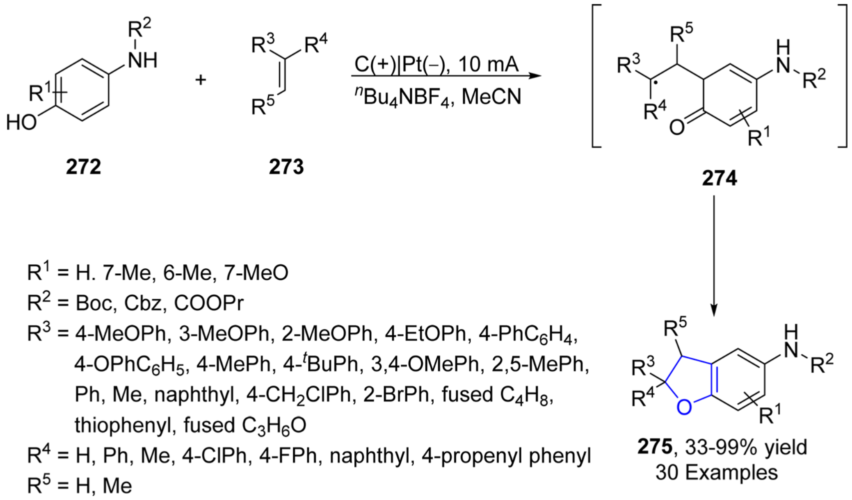
2.12. W-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Owing to their inexpensive and reusable characteristics, tungsten (W) catalysts are abundantly used in organic



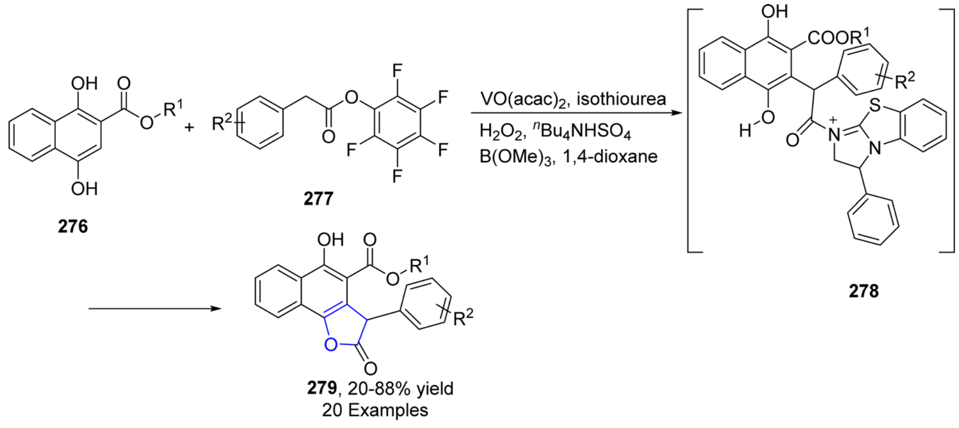
R^1 = H, Me, COOMe,
R^2 = 4-MeOPh, benzo[*d*][1,3]dioxole, SPh, 4-MePh, Ph
R^1, R^2 = (4a*S*,9a*S*)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole
R^3 = 5-OMe, 5-OMe-fused C_4H_4, 5-OCH_2Ph

Scheme 63 Synthesis of dihydrobenzofuran **271**.



R^1 = H. 7-Me, 6-Me, 7-MeO
R^2 = Boc, Cbz, COOPr
R^3 = 4-MeOPh, 3-MeOPh, 2-MeOPh, 4-EtOPh, 4-PhC$_6$H$_4$, 4-OPhC$_6$H$_5$, 4-MePh, 4-^{t}BuPh, 3,4-OMePh, 2,5-MePh, Ph, Me, naphthyl, 4-CH$_2$ClPh, 2-BrPh, fused C$_4$H$_8$, thiophenyl, fused C$_3$H$_6$O
R^4 = H, Ph, Me, 4-ClPh, 4-FPh, naphthyl, 4-propenyl phenyl
R^5 = H, Me

Scheme 64 Synthesis of dihydrobenzofurans **275**.



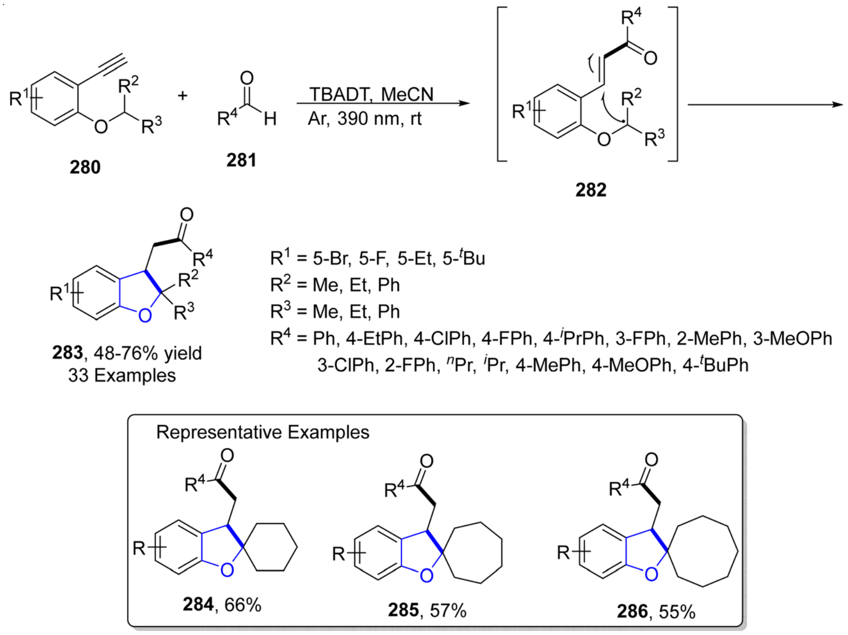
R^1 = H, 4-Me, 4-Ph, 4-F, 4-Cl, 4-Br, 4-CF$_3$, 4-CN, 4-OMe, 2-Br, 3-Br, 3-OMe, fused C$_4$H$_4$, thiophenyl
R^2 = C$_2$H$_4$Ph, CH$_2$-CH=CH$_2$, (CH$_2$)$_2$-CH(CH$_3$)$_2$, (CH$_2$)$_2$-1,3-dioxolane, CH$_2$-C$_2$H, CH$_2$-4-ClPh

Scheme 65 Synthesis of polycyclic dihydrobenzofuran **279**.

synthesis. Another visible-light promoted synthetic route to achieve dihydrobenzofurans was given in 2023 by Gowda[135] *et al.* For this purpose, diversely substituted aromatic aldehydes **281** were made to react with alkynyl aryl ethers **280** exploiting TBADT (tetrabutylammonium decatungstate), which is a photocatalyst, responsible for carrying out 1,5-hydrogen atom transfer. The reaction protocol involved the use of visible light (390 nm) in acetonitrile solvent to afford dihydrobenzofurans **283** (in 48–76% yield range) *via* the activation of C–H bond without any addition of additive. The plausible mechanism of this reaction was believed to include the excitation of photocatalyst *via* visible light, followed by the removal of proton from aromatic aldehydes **281** to give the acyl radical. The resulting radical was then assumed to execute the addition reaction with alkynyl aryl ethers **280** proceeded by 1,5-transfer of hydrogen atom to give rise to intermediate **282.** This intermediate then finally gave substituted dihydrobenzofurans **283** *via exo–dig* radical involving cyclization and subsequent reduction (Scheme 66).

2.13. Co-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Cobalt (Co)-based catalyst have high reducibility, high oxygen mobility and thermal stability due to which they are extensively studied and used in the field of organic synthesis. Tian[136] *et al.* in 2021 reported a facile one-pot, photosensitized and cobalt-catalyzed approach for the synthesis of 2,3-dihydrobenzofuran derivatives **289.** In their synthetic methodology, 2-propynolphenols **287** underwent semi-hydrogenation and intramolecular cyclization in the presence of a photosensitizer, *i.e.*, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ and a cobalt catalyst (Co(OAc)$_2$·4H$_2$O), to access 2,3-dihydrobenzofuran units **289.** This methodology covers diverse functionalities (18 examples) and gave moderate to excellent yields (54–98%). Phenolic hydroxyl



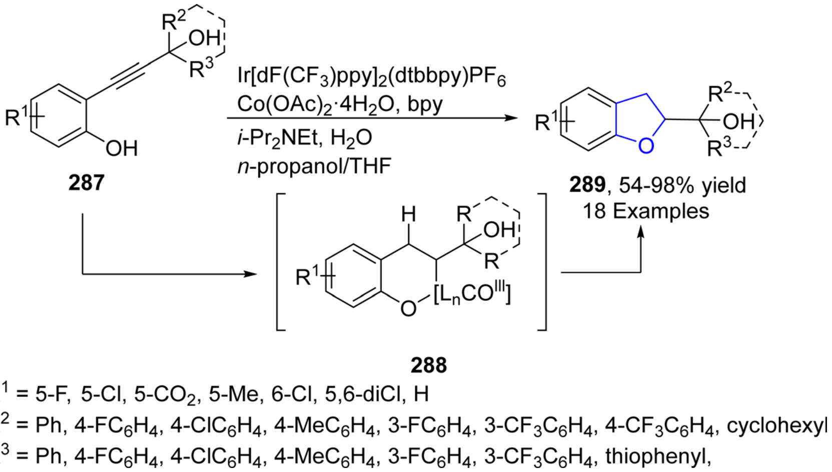
Scheme 66 Synthesis of dihydrobenzofuran derivatives **283**.

played a vital role for the intramolecular cyclization with (*Z*)-alkene, which was transformed from alkyne group of **287**. As per the suggested mechanism, activated Co species underwent hydrometallation with alkyne part of **287**, proceeded by protonation and oxidative addition (with phenolic hydroxyl group). The resulting intermediate was converted into intermediate **288** on migratory insertion and yielded the final products **289** *via* reductive elimination (Scheme 67).

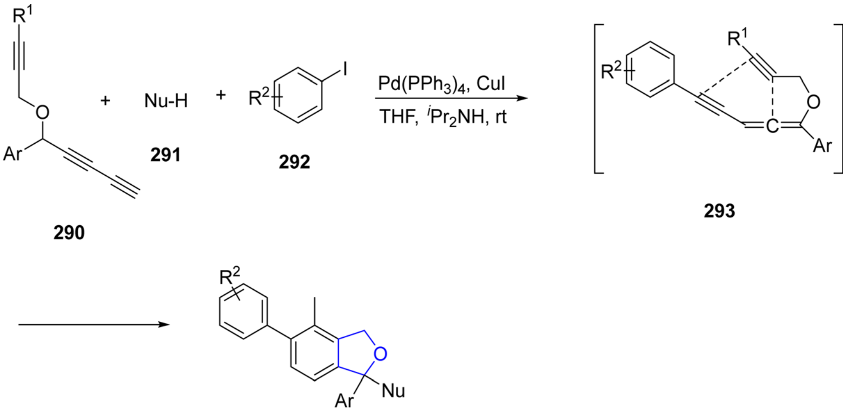
2.14. Dual metal-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

2.14.1. Pd and Cu-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives. Phthalans are structurally dihydrobenzofurans constituting organic scaffolds, which are of significant contribution in the pharmaceutical industry. In 2022, Huang[137] *et al.* reported a facile approach to procure a diverse range of substituted phthalans **294** utilizing Sonogashira coupling. Their synthetic strategy involved the reaction of substituted aryl halides **290**, nucleophiles **291** and substituted triynes **292** in the presence of catalytic amount of palladium tetrakis(triphenylphosphine) and copper iodide using diisopropyl amine as the base in tetrahydrofuran. The reaction was assumed to propagate *via* oxidative addition and palladium promoted coupling, followed by reductive elimination and base-catalyzed propargyl–allenyl isomerization to generate intermediate **293**. Intermediate **293** was then supposed to undergo PDDA cyclization, followed by subsequent regioselective nucleophilic addition to construct a wide variety of 1,3-dihydroisobenzofurans (phthalans) **294** in moderate to excellent yields (40–92%) (Scheme 68).

2.14.2. Pd and Ni-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives. Dual catalysis is one of the most



Scheme 67 Synthesis of dihydrobenzofuran derivatives **289**.

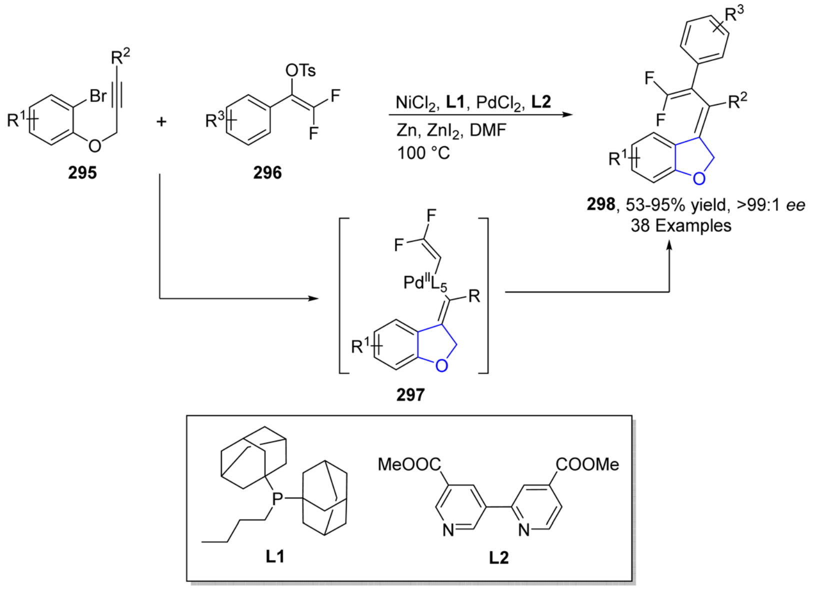


294, 40-86% yield
22 Examples

R^1 = Me, Ph, 4-OMePh, 4-ClPh, 4-MePh
R^2 = 4-COOMePh, 4-COMePh, 4-CNPh, 2-CNPh, 3-CF_3Ph, 3,5-ClPh
Ar = H, Ph, 3-ClPh, 3-MePh, 4-MePh, 4-FPh, furanyl, 4-MePh
Nu = NH^nBu, NH^tBu, NHEt, $NH(CH_2)_3Ph$, NEt_2, O^nBu, $O(CH_2)_3$-4BrPh, OC_3H_4Ph, morpholine

Scheme 68 Synthesis of substituted phthalans **294**.

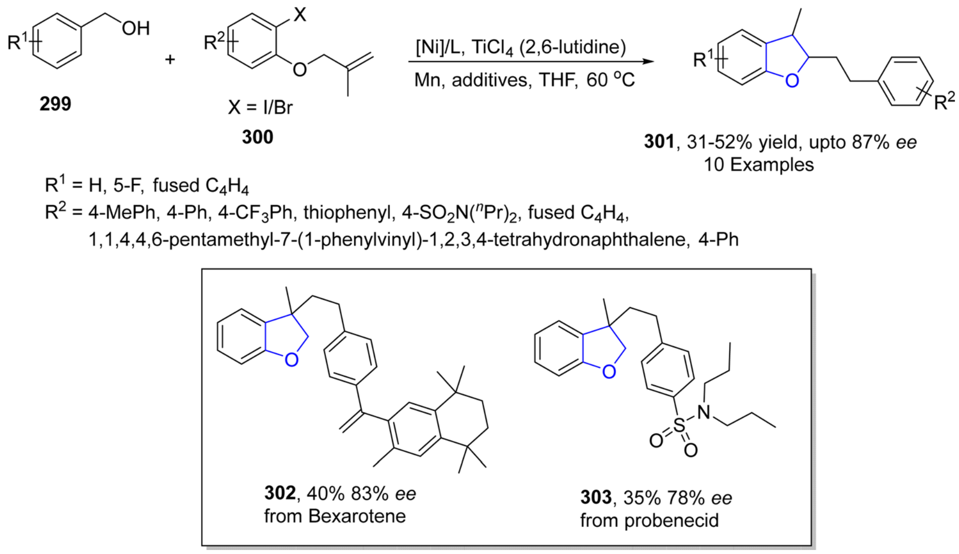
dynamic strategies for the advancement of chemical reactions in organic synthesis. Lian[138] *et al.* in 2022 devised a dual catalytic protocol to synthesize 2,3-dihydrobenzofurans **298** containing *gem*-difluorovinyl framework. In their synthetic approach, the coupling of *gem*-difluorovinyl tosylates **296** and alkynyl bromoarenes **295** occurred in the presence of Pd and Ni catalyst along with ZnI_2 (as an additive) and Zn (as reductant) in DMF at 100 °C. As interpreted by the proposed mechanism, alkynyl bromoarenes **295** underwent subsequent oxidative addition and cyclization process in the presence of Pd(0) species. Next, Ni(0)-catalyzed oxidative addition of *gem*-difluorovinyl tosylates **296** took place, proceeded by the transmetallation step to generate *gem*-difluorovinyl zinc intermediate, which interacted with Pd-mediated alkynyl



298, 53-95% yield, >99:1 *ee*
38 Examples

R^1 = 4-Me, 3-COOMe, 4-Cl, 4-F, 4-OMe, 4-^{t}Bu
R^2 = C_6H_5, 4-PhC_6H_4, 4-$C_2H_4TMSC_6H_4$, 4-$^tBuC_6H_4$, 4-$MeOC_6H_4$, 4-$CH_2CNC_6H_4$, 4-$COCH_3C_6H_4$, 4-$MeCOOC_6H_4$, 3-$CF_3OC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 3,4 fusedC_6H_4, 4-Cl-3-(4-ethoxybenzyl)benzene, (5-(4-F-phenyl)thiophen-2-yl)(*o*-tolyl)methanone, 4-(phenylsulfonyl)morpholine, 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane, thiophenyl, quinoline, benzo[d][1,3]dioxole
R^3 = 3,4-fusedC_6H_3, 4-Ph, 4-Me, 3-Me, 2,3diMe, 3-Cl, 4-OCF_3

Scheme 69 Synthesis of 2,3-dihydrobenzofurans **298**.



R^1 = H, 5-F, fused C_4H_4
R^2 = 4-MePh, 4-Ph, 4-CF_3Ph, thiophenyl, 4-$SO_2N(^nPr)_2$, fused C_4H_4,
1,1,4,4,6-pentamethyl-7-(1-phenylvinyl)-1,2,3,4-tetrahydronaphthalene, 4-Ph

Scheme 70 Synthesis of 2,3-dihydrobenzofurans **301**.

bromoarenes species to form intermediate **297**. This intermediate underwent reductive elimination to furnish the desired 2,3-dihydrobenzofuran derivative **298** (Scheme 69).

2.14.3. Ti and Ni-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives. Ni-catalyzed stereoselective reductive dicarbofunctionalization of alkenes is the most facile approach for the rapid generation of several asymmetric cyclic frameworks.[139] Similarly, various catalysts comprising of titanium (Ti) play a crucial role in the development of dihydrobenzofuran core structure.[140] In 2023, Zhao[141] *et al.* also utilized haloarene-substituted alkenes **300** for the asymmetric synthesis of dihydrobenzofurans **301**. They reacted aromatic rings-joined alkenes with substituted benzyl alcohols **299** by employing Ni(COD)$_2$ and titanium chloride (TiCl$_4$) as catalysts in the presence of ligand, manganese, 2,6-lutidine in tetrahydrofuran to achieve the enantioenriched dihydrobenzofurans **301** in 31–51% yield with 75–87% ee (Scheme 70). The synthetic strategy was also utilized to furnish the dihydrobenzofuran derivatives **302** and **303** from clinically approved drugs, *i.e.*, bexarotene (used against T-cell lymphoma cancer) and probenecid (used in the treatment of gout), respectively.

3 Conclusion

This review article elucidates the latest developments in the transition metal-catalyzed synthesis of polysubstituted dihydrobenzofuran derivatives. Due to their exemplary output, cost effectiveness, and diversification, transition metal-mediated one-pot synthesis involving cutting-edge methodologies, *i.e.*, multiple C–C/C–O bond-forming processes in an intermolecular or intramolecular approach, annulation and insertion reactions, have been rigorously explored towards the accomplishment of these heterocycles. Various transition metals, *i.e.*, Rh, Pd, Cu, Co, Ni, Fe, Ag, Au, W, Ir, Pt, V and Ru-catalyzed robust methodologies have been scrutinized towards the synthesis of 2,3-dihydrobenzofurans derivatives along with their mechanistic details. It is aimed that this communication, by providing a comprehensive perspective of the synthetic protocols available, will assist to provoke attention in the study of dihydrobenzofurans in pharmaceutical and medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

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References

1 A. Radadiya and A. Shah, Bioactive Benzofuran Derivatives: An insight on Iead Developments, Radioligands and Advances of the Last Decade, *Eur. J. Med. Chem.*, 2015, **97**, 356–376.

2 R. J. Nevagi, S. N. Dighe and S. N. Dighe, Biological and Medicinal Significance of Benzofuran, *Eur. J. Med. Chem.*, 2015, **97**, 561–581.

3 R. Munir, A. F. Zahoor, U. Nazeer, M. A. Saeed, A. Mansha, A. Irfan and M. U. Tariq, Gilman Reagent Toward the Synthesis of Natural Products, *RSC Adv.*, 2023, **13**(50), 35172–35208.

4 H. Qin, Z. Xu, Y. Cui and Y. Jia, Total Synthesis of (±)-Decursivine and (±)-Serotobenine: A Witkop

Photocyclization/Elimination/O-Michael Addition Cascade Approach, *Angew. Chem., Int. Ed.*, 2011, **19**(50), 4447–4449.

5 D. H. Wang and J. Q. Yu, Highly Convergent Total Synthesis of (+)-Lithospermic Acid *via* a Late-Stage Intermolecular C–H Olefination, *J. Am. Chem. Soc.*, 2011, **133**(15), 5767–5769.

6 Q. Huang, P. Wang, Y. Tian, N. Song, S. Ren, J. Tao, K. Hang and M. Li, Synthesis of (±)-Pterocarpin and its Thia-and Aza-Analogues in a Modular Manner, *Synlett*, 2015, **26**(10), 1385–1390.

7 Y. Natori, H. Tsutsui, N. Sato, S. Nakamura, H. Nambu, M. Shiro and S. Hashimoto, Asymmetric synthesis of Neolignans (−)-Epi-conocarpan and (+)-Conocarpan *via* Rh (II)-Catalyzed C−H Insertion Process and Revision of the Absolute Configuration of (−)-Epi-Conocarpan, *J. Org. Chem.*, 2009, **74**(11), 4418–4421.

8 C. W. am Ende, Z. Zhou and K. A. Parker, Total Synthesis of (±)-Bisabosqual A, *J. Am. Chem. Soc.*, 2013, **135**(2), 582–585.

9 N. E. Wright and S. A. Snyder, 9-Membered Carbocycle Formation: Development of Distinct Friedel–Crafts Cyclizations and Application to a Scalable Total Synthesis of (±)-Caraphenol A, *Angew. Chem., Int. Ed.*, 2014, **53**(13), 3409–3413.

10 S. Panthee, S. Takahashi, H. Takagi, T. Nogawa, E. Oowada, M. Uramoto and H. Osada, Furaquinocins I and J: Novel Polyketide Isoprenoid Hybrid Compounds From Streptomyces Reveromyceticus SN-593, *J. Antibiot.*, 2011, **64**(7), 509–513.

11 Y. F. Qiaos, K. Takeya, H. Itokawa and Y. Iitaka, Three Novel Naphthohydroquinone Dimers from Rubia Oncotricha, *Chem. Pharm. Bull.*, 1990, **38**(10), 2896–2898.

12 S. Eckhardt, Recent progress in the development of anticancer agents, *Curr. Med. Chem.: Anti-Cancer Agents*, 2002, **2**(3), 419–439.

13 I. Shahzadi, A. F. Zahoor, A. Rasul, N. Rasool, Z. Raza, S. Faisal, B. Parveen, S. Kamal, M. Zia-ur-Rehman and F. M. Zahid, Synthesis, anticancer, and computational studies of 1, 3, 4-oxadiazole-purine derivatives, *J. Heterocycl. Chem.*, 2020, **57**(7), 2782–2794.

14 I. Shahzadi, A. F. Zahoor, A. Rasul, A. Mansha, S. Ahmad and Z. R. Synthesis, hemolytic studies, and *in silico* modeling of novel acefylline–1, 2, 4-triazole hybrids as potential anti-cancer agents against MCF-7 and A549, *ACS Omega*, 2021, **6**(18), 11943–11953.

15 V. Gandin, P. Khalkar, J. Braude and A. P. Fernandes, Organic selenium compounds as potential chemotherapeutic agents for improved cancer treatment, *Free Radical Biol. Med.*, 2018, **127**, 80–97.

16 R. Akhtar, A. F. Zahoor, A. Rasul, M. Ahmad, M. N. Anjum, M. Ajmal and Z. Raza, Design, synthesis, *in silico* study and anticancer potential of novel n-4-piperazinyl-ciprofloxacin-aniline hybrids, *Pak. J. Pharm. Sci.*, 2019, **32**(5), 2215–2222.

17 T. Otani, Y. Sugimoto, Y. Aoyagi, Y. Igarashi, T. Furumai, N. Saito, T. Asao and T. Oki, New Cdc25B Tyrosine Phosphatase Inhibitors, Nocardiones A and B, Produced by Nocardia sp. TP-A0248: Taxonomy, Fermentation, Isolation, Structural Elucidation and Biological Properties, *J. Antibiot.*, 2000, **53**(4), 337–344.

18 W. Chen, X. D. Yang, Y. Li, L. J. Yang, X. Q. Wang, G. L. Zhang and H. B. Zhang, Design, Synthesis and Cytotoxic Activities of Novel Hybrid Compounds Between Dihydrobenzofuran and Imidazole, *Org. Biomol. Chem.*, 2011, **9**(11), 4250–4255.

19 S. Van Miert, S. Van Dyck, T. J. Schmidt, R. Brun, A. Vlietinck, G. Lemière and L. Pieters, Antileishmanial Activity, Cytotoxicity and QSAR Analysis of Synthetic Dihydrobenzofuran Lignans and Related Benzofurans, *Bioorg. Med. Chem.*, 2005, **13**(3), 661–669.

20 N. Negoro, S. Sasaki, S. Mikami, M. Ito, M. Suzuki, Y. Tsujihata, R. Ito, A. Harada, K. Takeuchi, N. Suzuki, J. Miyazaki, T. Santou, T. Odani, N. Kanzaki, M. Funami, T. Tanaka, A. Kogame, S. Matsunaga, T. Yasuma and Y. Momose, Discovery of TAK-875: A Potent, Selective, and Orally Bioavailable GPR40 agonist, *ACS Med. Chem. Lett.*, 2010, **1**(6), 290–294.

21 R. P. Tripathi, A. K. Yadav, A. Ajay, S. S. Bisht, V. Chaturvedi and S. K. Sinha, Application of Huisgen (3+ 2) Cycloaddition Reaction: Synthesis of 1-(2, 3-Dihydrobenzofuran-2-yl-methyl [1, 2, 3]-triazoles) and their Antitubercular Evaluations, *Eur. J. Med. Chem.*, 2010, **45**(1), 142–148.

22 J. E. Frampton, Prucalopride, *Drugs*, 2009, **69**, 2463–2476.

23 C. B. Chapleo, P. L. Myers, R. C. Butler, J. A. Davis, J. C. Doxey, S. D. Higgins, M. Myers, A. G. Roach and C. F. Smith, Alpha-Adrenoceptor Reagents. 2. Effects of Modification of the 1, 4-benzodioxan Ring System on Alpha-Adrenoreceptor Activity, *J. Med. Chem.*, 1984, **27**(5), 570–576.

24 Z. Chen, W. Huang, Y. Su, H. Jiang and W. Wu, Lewis/Brønsted Acid-Mediated Cyclization/Amidation of 1, 6-enynes with Nitriles: Access to 3-enamide Substituted Dihydrobenzofurans, *Chem. Commun.*, 2023, **59**(30), 4523–4526.

25 H. Rouh, Y. Tang, T. Xu, Q. Yuan, S. Zhang, J. Y. Wang, S. Jin, Y. Wang, J. Pan, H. L. Wood, J. D. Mcdodald and G. Li, Aggregation-induced synthesis (AIS): asymmetric synthesis *via* chiral aggregates, *Research*, 2022, **2022**, 9865108.

26 S. Zhou, B. Cai, C. Hu, X. Cheng, L. Li and J. Xuan, Visible Light and Base Promoted OH Insertion/Cyclization of *Para*-Quinone Methides with Aryl Diazoacetates: An Approach to 2, 3-Dihydrobenzofuran Derivatives, *Chin. Chem. Lett.*, 2021, **32**(8), 2577–2581.

27 M. Xiang, C. Y. Li, J. Zhang, Y. Zou, Z. C. Huang, W. S. Li, Y. Wang, F. Tian and L. X. Wang, Organocatalyst-promoted Diastereoselective and Enantioselective Michael Addition/Hemiketalization Reaction between Hydroxymaleimide and Quinone, *Asian J. Org. Chem.*, 2021, **10**(7), 1713–1717.

28 K. Röser, A. Scheucher, C. Mairhofer, M. Bechmann and M. Waser, Oxidative Decarboxylative Ammonium Hypoiodite-catalysed Dihydrobenzofuran Synthesis, *Org. Biomol. Chem.*, 2022, **20**(16), 3273–3276.

29 K. M. Dawood and T. Fuchigami, Electrochemical Partial Fluorination of Organic Compounds. 74. Efficient Anodic Synthesis of 2-Fluoro-and 2, 3-Difluoro-2, 3-dihydrobenzofuran Derivatives, *J. Org. Chem.*, 2004, **69**(16), 5302–5306.

30 K. S. O'Callaghan, D. Lynch, M. Baumann, S. G. Collins and A. R. Maguire, Flow Photolysis of Aryldiazoacetates Leading to Dihydrobenzofurans *Via* Intramolecular C–H Insertion, *Org. Biomol. Chem.*, 2023, **21**(23), 4770–4780.

31 L. Gonnard, A. Guérinot and J. Cossy, Transition Metal-Catalyzed α-Alkylation of Amines by C(sp^3)–H Bond Activation, *Tetrahedron*, 2019, **75**(2), 145–163.

32 T. R. Blum, Y. Zhu, S. A. Nordeen and T. P. Yoon, Photocatalytic Synthesis of Dihydrobenzofurans by Oxidative [3+ 2] Cycloaddition of Phenols, *Angew. Chem.*, 2014, **126**(41), 11236–11239.

33 S. S. Sakate, S. H. Shinde, G. B. Kasar, R. C. Chikate and C. V. Rode, Cascade Synthesis of Dihydrobenzofuran *via* Claisen Rearrangement of Allyl Aryl Ethers Using FeCl3/MCM-41 Catalyst, *J. Saudi Chem. Soc.*, 2018, **22**(4), 396–404.

34 M. C. Henry, H. M. Senn and A. Sutherland, Synthesis of Functionalized Indolines and Dihydrobenzofurans by Iron and Copper Catalyzed Aryl C–N and C–O Bond Formation, *J. Org. Chem.*, 2018, **84**(1), 346–364.

35 T. Ohmura, S. Kusaka, T. Torigoe and M. Suginome, Iridium-Catalyzed C(sp^3)–H Addition of Methyl Ethers across Intramolecular Carbon–Carbon Double Bonds Giving 2, 3-Dihydrobenzofurans, *Adv. Synth. Catal.*, 2019, **361**(19), 4448–4453.

36 C. Ni, J. Gao and X. Fang, Cu (i)-Catalyzed Asymmetric Intramolecular Addition of Aryl Pinacolboronic Esters to Unactivated Ketones: Enantioselective Synthesis of 2, 3-Dihydrobenzofuran-3-ol Derivatives, *Chem. Commun.*, 2020, **56**(17), 2654–2657.

37 Y. Li, W. Li, J. Tian, G. Huang and H. Lv, 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.

38 R. K Rit, K. Ghosh, R. Mandal and A. K. Sahoo, Ruthenium-Catalyzed Intramolecular Hydroarylation of Arenes and Mechanistic Study: Synthesis of Dihydrobenzofurans, Indolines, and Chromans, *J. Org. Chem.*, 2016, **81**(18), 8552–8560.

39 S. Agasti, S. Maity, K. J. Szabo and D. Maiti, Palladium-Catalyzed Synthesis of 2, 3-Disubstituted Benzofurans: An Approach Towards the Synthesis of Deuterium Labeled Compounds, *Adv. Synth. Catal.*, 2015, **357**(10), 2331–2338.

40 M. Szlosek-Pinaud, P. Diaz, J. Martinez and F. Lamaty, Efficient Synthetic Approach to Heterocycles Possessing the 3, 3-Disubstituted-2,3-Dihydrobenzofuran Skeleton *via* Diverse Palladium-Catalyzed Tandem Reactions, *Tetrahedron*, 2007, **63**(16), 3340–3349.

41 L. Yang, X. Liang, Y. Ding, X. Li, X. Li and Q. Zeng, Transition Metal-Catalyzed Enantioselective Synthesis of Chiral Five-and Six-Membered Benzo O-heterocycles, *Chem. Rec.*, 2023, **23**(11), e202300173.

42 T. Laurita, R. D'Orsi, L. Chiummiento, M. Funicello and P. Lupattelli, Recent advances in synthetic strategies to 2, 3-dihydrobenzofurans, *Synthesis*, 2020, **52**(10), 1451–1477.

43 A. B. Dapkekar, C. Sreenivasulu, D. Ravi Kishore and G. Satyanarayana, Recent advances towards the synthesis of dihydrobenzofurans and dihydroisobenzofurans, *Asian J. Org. Chem.*, 2022, **11**(5), e202200012.

44 P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, 3d transition metals for C–H activation, *Chem. Rev.*, 2018, **119**(4), 2192–2452.

45 T. W. Lyons and M. S. Sanford, Palladium-catalyzed Ligand-Directed C–H Functionalization Reactions, *Chem. Rev.*, 2010, **110**(2), 1147–1169.

46 S. Cui, Y. Zhang and Q. Wu, Rh (iii)-Catalyzed C–H Activation/Cycloaddition of Benzamides and Methylenecyclopropanes: Divergence in Ring Formation, *Chem. Sci.*, 2013, **4**(9), 3421–3426.

47 H. Zhang, S. Lin, H. Gao, K. Zhang, Y. Wang, Z. Zhou and W. Yi, Chemodivergent Assembly of *Ortho*-Functionalized Phenols with Tunable Selectivity *Via* Rhodium (III)-Catalyzed and Solvent-Controlled CH activation, *Commun. Chem.*, 2021, **4**(1), 81.

48 X. Song, K. Wang, L. Xue, H. Yu, X. Zhang, R. Lee and X. Fan, Coupling Partner-Dependent Unsymmetrical C–H Functionalization of N-phenoxyacetamides Leading to Sophisticated Spirocyclic Scaffolds, *Org. Chem. Front.*, 2022, **9**(17), 4583–4590.

49 L. Sun, Y. Zhao, B. Liu, J. Chang and X. Li, Rhodium III-Catalyzed Remote Difunctionalization of Arenes Assisted by a Relay Directing Group, *Chem. Sci.*, 2022, **13**(24), 7347–7354.

50 Y. Wei, H. Xu, F. Chen, H. Gao, Y. Huang and W. Yi and Zhou, Specific Assembly of Dihydrobenzofuran Frameworks *via* Rh (iii)-Catalysed C–H Coupling of *N*-Phenoxyacetamides with 2-alkenylphenols, *New J. Chem.*, 2022, **46**(12), 5705–5711.

51 W. Yu, C. Chen, L. Feng, T. Xia, C. Shi, Y. Yang and B. Zhou, Rhodium (III)-Catalyzed Asymmetric 1, 2-Carboamidation of Alkenes Enables Access to Chiral 2, 3-Dihydro-3-Benzofuranmethanamides, *Org. Lett.*, 2022, **24**(9), 1762–1767.

52 N. Sinha, P. Mistry, S. Das, T. Datta and B. Roy, Intramolecular Hydroarylation of Arenes *via* Imidazole-Directed C–H Activation in Aqueous Methanol Using Rhodium (III) as the Catalyst and Mechanistic Study, *J. Org. Chem.*, 2023, **88**, 8969–8983.

53 Y. Wang and D. M. Du, Recent Advances in Organocatalytic Asymmetric Oxa-Michael Addition Triggered Cascade Reactions, *Org. Chem. Front.*, 2020, **7**(20), 3266–3283.

54 D. X. Zhu, J. G. Liu and M. H. Xu, Stereodivergent Synthesis of Enantioenriched 2, 3-Disubstituted Dihydrobenzofurans *via* a One-Pot C–H Functionalization/Oxa-Michael Addition Cascade, *J. Am. Chem. Soc.*, 2021, **143**(23), 8583–8589.

55 H. M. Davies and R. E. Beckwith, Catalytic Enantioselective C–H Activation by Means of Metal–Carbenoid-Induced C–H Insertion, *Chem. Rev.*, 2003, **103**(8), 2861–2904.

56 A. Padwa and S. F. Hornbuckle, Ylide Formation from the Reaction of Carbenes and Carbenoids with Heteroatom Lone Pairs, *Chem. Rev.*, 1991, **91**(3), 263–309.

57 S. E. Reisman, R. R. Nani and S. Levin, Buchner and beyond: Arene cyclopropanation as applied to natural product total synthesis, *Synlett*, 2011, **2011**(17), 2437–2442.

58 A. Tinoco, V. Steck, V. Tyagi and R. Fasan, Highly Diastereo- and Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes *via* Myoglobin-Catalyzed Transfer of Trifluoromethylcarbene, *J. Am. Chem. Soc.*, 2017, **139**(15), 5293–5296.

59 X. Zhang, P. Sivaguru, G. Zanoni, X. Han, M. Tong and X. Bi, Catalytic Asymmetric C (sp^3)–H Carbene Insertion Approach to Access Enantioenriched 3-fluoroalkyl 2, 3-Dihydrobenzofurans, *ACS Catal.*, 2021, **11**(22), 14293–14301.

60 A. M. Buckley, D. C. Crowley, T. A. Brouder, A. Ford, U. B. Rao Khandavilli, S. E. Lawrence and A. R. Maguire, Dirhodium Carboxylate Catalysts from 2-Fenchyloxy or 2-Menthyloxy Arylacetic Acids: Enantioselective C–H Insertion, Aromatic Addition and Oxonium Ylid Formation/Rearrangement, *ChemCatChem*, 2021, **13**(20), 4318–4324.

61 K. Hong, S. Dong, X. Xu, Z. Zhang, T. Shi, H. Yuan, X. Xu and W. Hu, Enantioselective Intermolecular Mannich-type Interception of Phenolic Oxonium Ylide for the Direct Assembly of Chiral 2, 2-disubstituted Dihydrobenzofurans, *ACS Catal.*, 2021, **11**(12), 6750–6756.

62 K. Hong, X. Yang, Z. Zhang, X. Xie, X. Lv, X. Xu and W. Hu, Diastereoselective Aldol-Type Interception of Phenolic Oxonium Ylides for the Direct Assembly of 2, 2-disubstituted Dihydrobenzofurans, *Org. Biomol. Chem.*, 2022, **20**(22), 4635–4639.

63 X. Zhong, S. Lin, H. Gao, F. X. Liu, Z. Zhou and W. Yi, Rh (III)-Catalyzed Redox-Neutral C–H Activation/[3+ 2] Annulation of *N*-phenoxy Amides with Propargylic Monofluoroalkynes, *Org. Lett.*, 2021, **23**(6), 2285–2291.

64 A. Singh, A. Dey and C. M. Volla, Rh (III)-Catalyzed Stereoselective C–C Bond Cleavage of ACPs with N-Phenoxyacetamides: The Critical Role of the Nucleophilic Directing Group, *J. Org. Chem.*, 2021, **86**(15), 10474–10483.

65 U. Nazeer, A. Mushtaq, A. F. Zahoor, F. Hafeez, I. Shahzadi and R. Akhtar, Cloke–Wilson Rearrangement: A Unique Gateway to Access Five-Membered Heterocycles, *RSC Adv.*, 2023, **13**(50), 35695–35732.

66 D. J. Paymode and I. Sharma, Rhodium-Catalyzed [3+ 2]-Annulation of *Ortho*-Diazoquinones with Enol Ethers: Diversity-Oriented Total Synthesis of Aflatoxin B2, *Eur. J. Org Chem.*, 2021, **2021**(13), 2034–2040.

67 A. F. Zahoor, M. Yousaf, R. Siddique, S. Ahmad, S. A. R. Naqvi and S. M. A. Rizvi, Synthetic strategies toward the synthesis of enoxacin-, levofloxacin-, and gatifloxacin-based compounds: A review, *Synth. Commun.*, 2017, **47**(11), 1021–1039.

68 S. Ahmad, A. F. Zahoor, S. A. R. Naqvi and M. Akash, Recent trends in ring opening of epoxides with sulfur nucleophiles, *Mol. Diversity*, 2018, **22**(1), 191–205.

69 J. Jiang, J. Liu, Z. Yang, L. Zheng and Z. Q. Liu, Three-Component Synthesis of Benzofuran-3 (2*H*)-ones with Tetrasubstituted Carbon Stereocenters *via* Rh (III)-Catalyzed C–H/C–C Bond Activation and Cascade Annulation, *Adv. Synth. Catal.*, 2022, **364**(15), 2540–2545.

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

71 M. L. Han, W. Huang, Y. W. Liu, M. Liu, H. Xu, H. Xiong and H. X. Dai, Pd-Catalyzed Asymmetric Dearomatization of Indoles *via* Decarbonylative Heck-type Reaction of Thioesters, *Org. Lett.*, 2020, **23**(1), 172–177.

72 Y. Madich, R. Álvarez and J. M. Aurrecoechea, Palladium Catalyzed Regioselective 5-Exo-O-Cyclization/Oxidative Heck Cascades from o-Alkynylbenzamides and Electron-Deficient Alkenes, *Eur. J. Org Chem.*, 2014, **2014**(28), 6263–6271.

73 Y. Wu, B. Xu, G. Zhao, Z. Pan, Z. M. Zhang and J. Zhang, Palladium/Xu-Phos Catalyzed Enantioselective Tandem Heck/Cacchi Reaction of Unactivated Alkenes, *Chin. J. Chem.*, 2021, **39**(12), 3255–3260.

74 C. Sreenivasulu and G. Satyanarayana, Time and Temperature Dependent Palladium-Catalyzed Stereo-and Regioselective Alkoxy-arylation of Triple Bonds: Synthesis of (E)/(Z)-1, 1-Disubstituted-3-(1-Phenylalkylidene)-1, 3-dihydroisobenzofurans, *J. Org. Chem.*, 2021, **86**(12), 8182–8196.

75 C. Fang, Q. Wang, B. Xu, Z. Zhang and J. Zhang, Palladium/XuPhos-Catalyzed Enantioselective Cascade Heck/Intermolecular C(sp^2)–H Alkylation Reaction, *Chem. Sci.*, 2024, **15**, 5573–5580.

76 Y. Wu, L. Wu, Z. M. Zhang, B. Xu, Y. Liu and J. Zhang, Enantioselective Difunctionalization of Alkenes by a Palladium-Catalyzed Heck/borylation Sequence, *Chem. Sci.*, 2022, **13**(7), 2021–2025.

77 J. M. Guo, Z. Y. Mao, C. H. Liu, S. Y. Yang and B. G. Wei, Palladium-Catalyzed Sequential Heck Reactions of Olefin-Tethered Aryl Iodides with Alkenes, *J. Org. Chem.*, 2022, **87**(17), 11838–11845.

78 K. Babar, A. F. Zahoor, S. Ahmad and R. Akhtar, Recent synthetic strategies toward the synthesis of spirocyclic compounds comprising six-membered carbocyclic/heterocyclic ring systems, *Mol. Diversity*, 2021, **25**, 2487–2532.

79 A. D. Marchese, A. G. Durant and M. Lautens, A Modular Approach for the Palladium-Catalyzed Synthesis of Bis-Heterocyclic Spirocycles, *Org. Lett.*, 2021, **24**(1), 95–99.

80 Y. Kang, J. L. Lu, Z. Zhang, Y. K. Liang, A. J. Ma and J. B. Peng, Palladium-Catalyzed Intramolecular Heck/Aminocarbonylation of Alkene-Tethered Iodobenzenes with Nitro Compounds: Synthesis of Carbamoyl-

Substituted Benzoheterocycles, *J. Org. Chem.*, 2022, **88**(8), 5097–5107.

81 Y. Tu, B. Xu, Q. Wang, H. Dong, Z. M. Zhang and J. Zhang, Palladium/TY-Phos-Catalyzed Asymmetric Heck/Tsuji–Trost Reaction of o-Bromophenols with 1, 3-Dienes, *J. Am. Chem. Soc.*, 2023, **145**(8), 4378–4383.

82 A. Tinoco, V. Steck, V. Tyagi and R. Fasan, Highly Diastereo- and Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes *via* Myoglobin-Catalyzed Transfer of Trifluoromethylcarbene, *J. Am. Chem. Soc.*, 2017, **139**(15), 5293–5296.

83 M. Ding, P. Ou, X. Li, Y. Yu, M. Niu, Y. Yang, Y. Huang, W. Zhi-Xiang and X. Huang, Alkyne Insertion Enabled Vinyl to Acyl 1, 5-Palladium Migration: Rapid Access to Substituted 5-Membered-Dihydrobenzofurans and Indolines, *Angew. Chem., Int. Ed.*, 2023, **62**(18), e202300703.

84 R. V. Rozhkov and R. C. Larock, Synthesis of Dihydrobenzofurans *via* Palladium-Catalyzed Annulation of 1, 3-dienes by o-iodoaryl Acetates, *J. Org. Chem.*, 2010, **75**(12), 4131–4134.

85 F. Zhou, C. Li, M. Li, Y. Jin, H. Jiang, Y. Zhang and W. Wu, Synthesis of 2-isoxazolyl-2, 3-Dihydrobenzofurans *via* Palladium-Catalyzed Cascade Cyclization of Alkenyl Ethers, *Chem. Commun.*, 2021, **57**(39), 4799–4802.

86 K. E. Houghtling, A. M. Canfield and S. M. Paradine, Convergent Synthesis of Dihydrobenzofurans *via* Urea Ligand-Enabled Heteroannulation of 2-Bromophenols with 1, 3-Dienes, *Org. Lett.*, 2022, **24**(31), 5787–5790.

87 H. Sun, H. He, S. F. Ni and W. Guo, Asymmetric (4+ 1) Annulations by Cascade Allylation and Transient σ-Alkyl-Pd (II) Initiated Allylic Csp^3–H Activation, *Angew. Chem., Int. Ed.*, 2023, **62**(51), e202315438.

88 Z. Wu, Z. Wu, X. Sun, W. Qi, Z. Zhang and Y. Zhang, Palladium-Catalyzed Intramolecular Cross-Coupling of Unactivated C(sp^3)–H and C(sp^2)–H Bonds, *Org. Lett.*, 2021, **23**(18), 7161–7165.

89 P. M. Reddy, K. Ramachandran and P. Anbarasan, Palladium-Catalyzed Diastereoselective Synthesis of 2, 2, 3-trisubstituted Dihydrobenzofurans *via* Intramolecular Trapping of O-ylides with Activated Alkenes, *J. Catal.*, 2021, **396**, 291–296.

90 N. Bortolamei, A. A. Isse, V. B. Di Marco, A. Gennaro and K. Matyjaszewski, Thermodynamic Properties of Copper Complexes Used as Catalysts in Atom Transfer Radical Polymerization, *Macromolecules*, 2010, **43**(22), 9257–9267.

91 M. L. Rao and S. S. Islam, Copper-Catalyzed Synthesis of 1-(2-benzofuryl)-N-heteroarenes from o-hydroxy-gem-(dibromovinyl) benzenes and N-heteroarenes, *Org. Biomol. Chem.*, 2021, **19**(41), 9076–9080.

92 S. A. Morris, J. Wang and N. Zheng, The Prowess of Photogenerated Amine Radical Cations in Cascade Reactions: From Carbocycles to Heterocycles, *Acc. Chem. Res.*, 2016, **49**(9), 1957–1968.

93 T. Y. Zheng, Y. Q. Zhou, N. Yu, Y. L. Li, T. Wei, L. Peng, Y. Ling, K. Jiang and Y. Wei, Deconstructive Insertion of Oximes into Coumarins: Modular Synthesis of Dihydrobenzofuran-Fused Pyridones, *Org. Lett.*, 2022, **24**(12), 2282–2287.

94 M. Ríos-Gutiérrez and L. R. Domingo, Unravelling the mysteries of the [3+ 2] cycloaddition reactions, *Eur. J. Org Chem.*, 2019, **2019**(2–3), 267–282.

95 Z. R. Jing, D. D. Liang, J. M. Tian, F. M. Zhang and Y. Q. Tu, Enantioselective Construction of 2-Aryl-2, 3-Dihydrobenzofuran Scaffolds Using Cu/SPDO-Catalyzed [3+ 2] Cycloaddition, *Org. Lett.*, 2021, **23**(4), 1258–1262.

96 J. X. Zhu, J. M. Tian, Y. Y. Chen, X. J. Hu, X. Han, W. Chen, Z. Yang, X. Bao, X. Ye, H. Chen, F. M. Zhang, H. Wang and Y. Q. Tu, Enantioselective Synthesis of 2, 3, 3a, 8a-Tetrahydrofuro [2, 3-*b*] benzofuran Scaffolds Enabled by Cu (II)/SPDO-Catalyzed [3+ 2] Cycloaddition of 2, 3-Dihydrofuran and Quinone Esters, *J. Org. Chem.*, 2023, **88**(20), 14670–14675.

97 G. Sui, T. Li, B. Zhang, R. Wang, H. Hao and W. Zhou, Recent advances on synthesis and biological activities of aurones, *Bioorg. Med. Chem.*, 2021, **29**, 115895.

98 A. P. Devi, J. Pandey, U. Bhardwaj, N. Dhingra, R. Kant and K. L. Ameta, Green Synthesis and *in silico*, Neuraminidase Study of Some Substituted 2-Benzylidene-1-Benzofuran-3-Ones, *SSRN*, 2021, DOI: **10.2139/ssrn.3911206**.

99 K. Mitsudo, Y. Kobashi, K. Nakata, Y. Kurimoto, E. Sato, H. Mandai and S. Suga, Cu-Catalyzed Dehydrogenative C–O Cyclization for the Synthesis of Furan-Fused Thienoacenes, *Org. Lett.*, 2021, **23**(11), 4322–4326.

100 C. Liu, D. Liu and A. Lei, Recent advances of transition-metal catalyzed radical oxidative cross-couplings, *Acc. Chem. Res.*, 2014, **47**(12), 3459–3470.

101 K. Dong, C. Y. Zhao, X. J. Wang, L. Z. Wu and Q. Liu, Bioinspired Selective Synthesis of Heterodimer 8–5′ or 8–O–4′ Neolignan Analogs, *Org. Lett.*, 2021, **23**(7), 2816–2820.

102 V. P. Ananikov, Nickel: The “Spirited Horse” of Transition Metal Catalysis, *ACS Catal.*, 2015, **5**(3), 1964–1971.

103 F. Yang, Y. Jin and C. Wang, Nickel-catalyzed asymmetric intramolecular reductive Heck reaction of unactivated alkenes, *Org. Lett.*, 2019, **21**(17), 6989–6994.

104 A. Cerveri, R. Giovanelli, D. Sella, R. Pedrazzani, M. Monari, O. N. Faza, O. C. S. Lopez and M. Bandini, Enantioselective CO$_2$ Fixation *via* a Heck-Coupling/Carboxylation Cascade Catalyzed by Nickel, *Chem.–Eur. J.*, 2021, **27**(28), 7657–7662.

105 M. Bhardwaj, B. Rasool and D. Mukherjee, Ni-Catalyzed Domino Transformation of Enopyranoses and 2-iodo phenols/anilines to Pyrano Cis Fused Dihydrobenzofurans/indoles, *Chem. Commun.*, 2022, **58**(50), 7038–7041.

106 S. Xu, K. Wang and W. Kong, Ni-Catalyzed Reductive Arylacylation of Alkenes Toward Carbonyl-Containing Oxindoles, *Org. Lett.*, 2019, **21**(18), 7498–7503.

107 Y. Jin, P. Fan and C. Wang, Nickel-Catalyzed Reductive Asymmetric Aryl-Acylation and Aryl-Carbamoylation of Unactivated Alkenes, *CCS Chem.*, 2022, **4**(5), 1510–1518.

108 Z. Lin, Y. Jin, W. Hu and C. Wang, Nickel-Catalyzed Asymmetric Reductive Aryl-Allylation of Unactivated Alkenes, *Chem. Sci.*, 2021, **12**(19), 6712–6718.

109 H. Q. Geng, W. Wang and X. F. Wu, Nickel-Catalyzed Carbonylative Synthesis of Dihydrobenzofurans, *Catal. Commun.*, 2021, **148**, 106170.

110 M. He, Y. Sun and B. Han, Green Carbon Science: Efficient Carbon Resource Processing, Utilization, and Recycling Towards Carbon Neutrality, *Angew. Chem.*, 2022, **134**(15), e202112835.

111 C. Déjardin, A. Renou, J. Maddaluno and M. Durandetti, Nickel-Catalyzed Electrochemical Cyclization of Alkynyl Aryl Iodide and the Domino Reaction with Aldehydes, *J. Org. Chem.*, 2021, **86**(13), 8882–8890.

112 X. S. Li, D. T. Xu, Z. J. Niu, M. Li, W. Y. Shi, C. T. Wang, W. X. Wei and Y. M. Liang, Gold-Catalyzed Tandem Annulations of Pyridylhomopropargylic Alcohols with Propargyl Alcohols, *Org. Lett.*, 2021, **23**(3), 832–836.

113 N. Morita, H. Chiaki, K. Tanaka III, Y. Hashimoto, O. Tamura and N. Krause, Sustainable Chemical Synthesis of 2, 3-Dihydrobenzofurans/1, 2, 3-Trisubstituted Indanes in Water using a Permethylated β-Cyclodextrin-Tagged N-Heterocyclic Carbene–Gold Catalyst, *Synlett*, 2023, **34**(12), 1425–1432.

114 D. Prochowicz, A. Kornowicz and J. Lewiński, Interactions of Native Cyclodextrins with Metal Ions and Inorganic Nanoparticles: Fertile Landscape for Chemistry and Materials science, *Chem. Rev.*, 2017, **117**(22), 13461–13501.

115 Y. J. Wang, Y. Zhang, Z. Qiang, J. Y. Liang and Z. Chen, Gold Catalyzed Efficient Preparation of Dihydrobenzofuran from 1, 3-enyne and Phenol, *Chem. Commun.*, 2021, **57**(94), 12607–12610.

116 W. Du, R. Yang, J. Wu and Z. Xia, Flexible Synthesis of Benzofuranones from *ortho*-Alkynyl Phenols or Benzofurans, *Eur. J. Org Chem.*, 2023, **26**(8), e202201497.

117 S. Sau, K. Mukherjee, K. Kondalarao, V. Gandon and A. K. Sahoo, Probing Chiral Sulfoximine Auxiliaries in Ru (II)-Catalyzed One-Pot Asymmetric C–H Hydroarylation and Annulations with Alkynes, *Org. Lett.*, 2023, **25**(42), 7667–7672.

118 N. Pannilawithana, B. Pudasaini, M. H. Baik and C. S. Yi, Experimental and Computational Studies on the Ruthenium-Catalyzed Dehydrative C–H Coupling of Phenols with Aldehydes for the Synthesis of 2-Alkylphenol, Benzofuran, and Xanthene Derivatives, *J. Am. Chem. Soc.*, 2021, **143**(33), 13428–13440.

119 J. Phukon, P. Bhorali, S. Changmai and S. Gogoi, Hydroxyl-Directed Ru (II)-Catalyzed Synthesis of Fused Dihydrofurans Using 1, 4-Dioxane and Sulfoxonium Ylides as Annulating Agents, *Org. Lett.*, 2023, **25**(1), 215–219.

120 F. Yuan, D. M. Yan, P. P. Gao, D. Q. Shi, W. J. Xiao and J. R. Chen, Photoredox-Catalyzed Multicomponent Cyclization of 2-Vinyl Phenols, N-Alkoxypyridinium Salts, and Sulfur Ylides for Synthesis of Dihydrobenzofurans, *ChemCatChem*, 2021, **13**(2), 543–547.

121 Y. Liao, F. Liu and Z. J. Shi, Recent Progress in the Oxidative Coupling of Unactivated Csp^3–H Bonds with Other C–H Bonds, *Chem. Commun.*, 2021, **57**(98), 13288–13296.

122 S. Kusaka, T. Ohmura and M. Suginome, Iridium-Catalyzed Enantioselective Intramolecular Cross-Dehydrogenative Coupling of Alkyl Aryl Ethers Giving Enantioenriched 2, 3-Dihydrobenzofurans, *Chem. Lett.*, 2022, **51**(6), 601–604.

123 T. Shibata, S. Takayasu, S. Yuzawa and T. Otani, Rh (III)-Catalyzed C–H Bond Activation along with “Rollover” for the Synthesis of 4-Azafluorenes, *Org. Lett.*, 2012, **14**(19), 5106–5109.

124 K. Sakamoto and T. Nishimura, Enantioselective Synthesis of 3-substituted Dihydrobenzofurans Through Iridium-Catalyzed Intramolecular Hydroarylation, *Org. Biomol. Chem.*, 2021, **19**(3), 684–690.

125 T. Ohmura, S. Kusaka and M. Suginome, Iridium-Catalyzed Enantioselective Intramolecular Hydroarylation of Allylic Aryl Ethers Devoid of a Directing Group on the Aryl Group, *Chem. Commun.*, 2021, **57**(99), 13542–13545.

126 K. C. Majumdar, N. De, T. Ghosh and B. Roy, Iron-catalyzed synthesis of heterocycles, *Tetrahedron*, 2014, **70**(33), 4827–4868.

127 M. A. Bashir, X. Chen, T. Wang, H. Guo and H. Zhai, Synthesis of Cyclopenta[*b*]Benzofurans *via* Biomimetic Oxidative Phenol–enamine [3 + 2] Cycloaddition, *Org. Chem. Front.*, 2023, **10**(5), 1213–1218.

128 H. Zhang, B. Wang, H. Xu, F. Y. Li and J. Y. Wang, Synthesis of Naphthodihydrofurans *via* an Iron (iii)-Catalyzed Reduction Radical Cascade Reaction, *Org. Chem. Front.*, 2021, **8**(21), 6019–6025.

129 L. Guo, G. Chen, H. Li, C. H. Tung and Y. Wang, Visible-Light-Driven [3+ 2] Cyclization of Phenols with Indoles and Olefins Using Recyclable Ag_3PO_4 Nanoparticles, *Green Chem.*, 2023, **25**(18), 7102–7108.

130 H. J. Dias, M. L. Rodrigues and A. E. Crotti, Optimization of the Reaction Conditions for the Synthesis of Dihydrobenzofuran Neolignans, *J. Braz. Chem. Soc.*, 2021, **32**, 20–28.

131 J. Huo, Z. Wang, C. Oberschelp, G. Guillén-Gosálbez and S. Hellweg, Net-zero transition of the global chemical industry with CO_2-feedstock by 2050: feasible yet challenging, *Green Chem.*, 2023, **25**(1), 415–430.

132 K. Okamoto, N. Shida and M. Atobe, Electrochemical [3+ 2] Cycloaddition Proceeding at Low Electrolyte Concentration in Laminar-Flow Microreactor, *ChemElectroChem*, 2023, e202300386, DOI: **10.1002/celc.202300386**.

133 Y. H. Yang, Y. F. Tan, Y. N. Zhao, Y. H. He and Z. Guan, Electrosynthesis of 5-Aminocoumaran Derivatives from Olefins and Aminophenols, *Org. Lett.*, 2023, **25**(46), 8205–8209.

134 H. Wang, Y. Zhou, Y. Xie, Y. Liu, Y. Li, H. Zhang and J. Long, Synthesis of Functionalized 3-Aryl-3H-benzofuranone Derivatives from Aryl Acetate *via* [3+ 2] Annulation of 1, 4-Dihydroxy-2-naphthoic Acid Ester, *Org. Biomol. Chem.*, 2023, **21**(8), 1821–1826.

135 P. S. Gowda, D. S. Sharada and G. Satyanarayana, A TBADT Photocatalyst-Enabled Radical-Induced Cyclization Pathway to Access Functionalized Dihydrobenzofurans, *Chem. Commun.*, 2023, **59**(59), 9094–9097.

136 W. F. Tian, Y. Zhu, Y. Q. He, M. Wang, X. R. Song, J. Bai and Q. Xiao, Hydroxyl Assisted, Photoredox/Cobalt Co-catalyzed Semi-Hydrogenation and Tandem Cyclization of o-Alkynylphenols for Access to 2, 3-Dihydrobenzofurans, *Adv. Synth. Catal.*, 2021, **363**(3), 730–736.

137 W. Huang, H. Wang, B. Liu, R. Shen and S. Zhu, Synthesis of 1, 1, 4, 5-Tetrasubstituted Phthalans *via* Pd-Catalyzed Three-Component Reactions of Haloarenes, Alkynes, and Protic Nucleophiles, *Org. Lett.*, 2022, **24**(47), 8651–8656.

138 H. Sun, B. Xiong, Y. Yang, J. Liu, X. Zhang and Z. Lian, Gem-Difluorovinylation of Alkynyl Bromoarenes *via* Dual Nickel-/Palladium-Catalyzed Cross-Electrophile Coupling, *Org. Chem. Front.*, 2022, **9**(2), 305–310.

139 K. E. Poremba, S. E. Dibrell and S. E. Reisman, Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions, *ACS Catal.*, 2020, **10**(15), 8237–8246.

140 J. Wu, Y. Liu and M. C. Kozlowski, Visible-Light TiO_2-Catalyzed Synthesis of Dihydrobenzofurans by Oxidative [3+ 2] Annulation of Phenols with Alkenyl Phenols, *Chem. Sci.*, 2024, DOI: 10.1039/D4SC00723A.

141 C. Zhao, Z. Ge, J. Hu, H. Tian and X. Wang, Enantioselective Reductive Aryl-Benzylation of Alkenes by a Nickel-Titanium Bimetallic System, *Cell Rep.*, 2023, **4**(7), DOI: 10.1016/j.xcrp.2023.101474.