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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.

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## 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> Several bioactive natural products are composed of the

2,3-dihydrobenzofuran framework, such as (+)-decurvivine **3**,<sup>4</sup> (+)-lithospermic acid **4**,<sup>5</sup> pterocarpan **5**,<sup>6</sup> (+)-conocarpan **6**,<sup>7</sup> bisabosqual A **7**,<sup>8</sup> and caraphenol A **8**,<sup>9</sup> 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.<sup>11</sup> Cancer is one of the most prevailing and deadly diseases, and researchers are undertaking untiring efforts to discover and develop efficient anti-cancer agents.<sup>12–16</sup> (–)-Nocardione **11** (ref. 17) is a Cdc25B tyrosine phosphatase inhibitor that has been observed to display cytotoxic activities (Fig. 2).

Moreover, there are many synthetic dihydrobenzofuran derivatives demonstrating a variety of intriguing medicinal properties, including the imidazolium compound (cytotoxic) **13**,<sup>18</sup> diesters (anti-leishmaniasis) **14**,<sup>19</sup> GPR4 agonist **15**,<sup>20</sup> triazole (antitubercular) **16**,<sup>21</sup> and the drugs prucalopride **17** (used to treat constipation)<sup>22</sup> and efavroxan **18** ( $\alpha_2$ -adrenoceptor antagonist)<sup>23</sup> (Fig. 3).

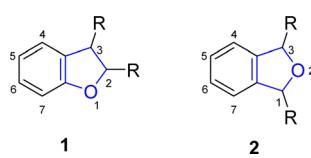


Fig. 1 General structure of dihydrobenzofuran **1** and dihydrosobenzofuran **2**.

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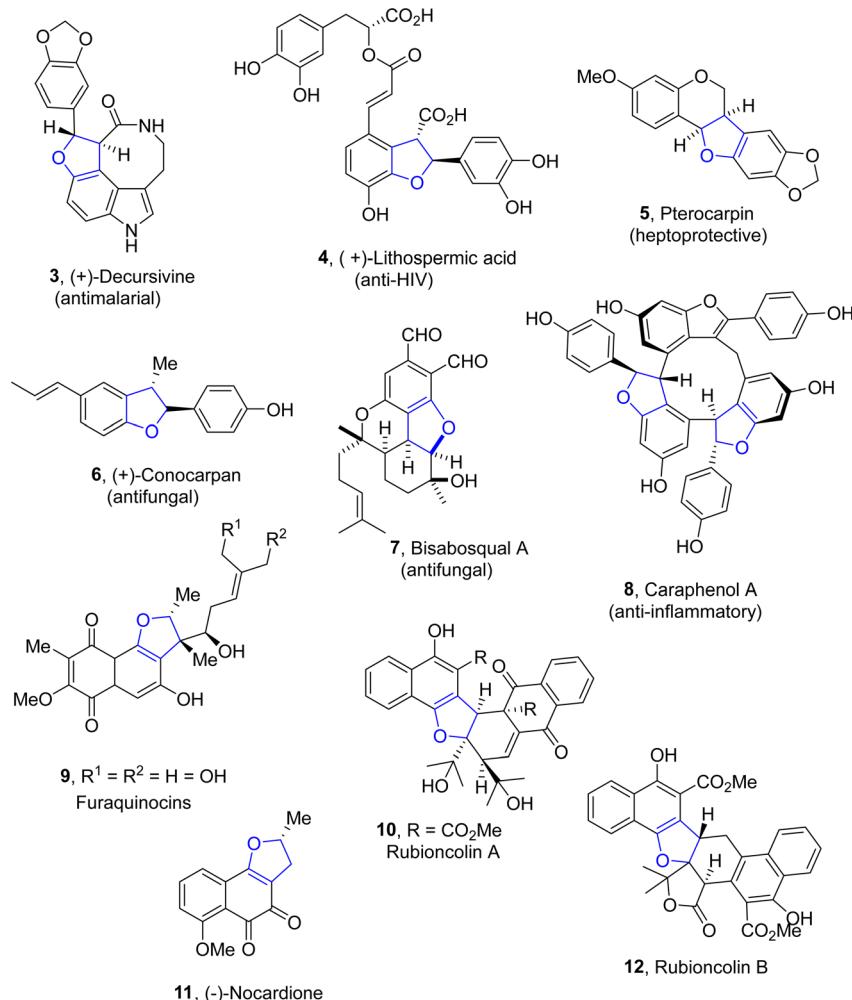


Fig. 2 Structures of some naturally occurring dihydrobenzofurans.

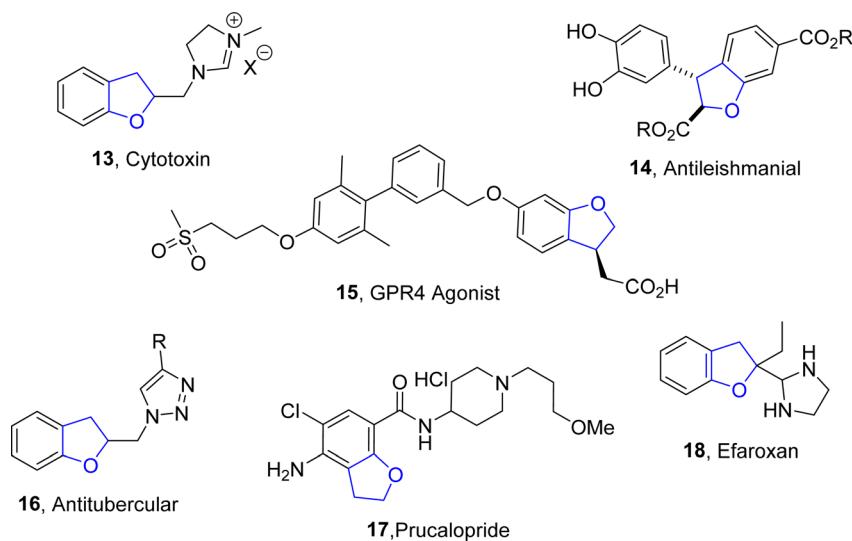


Fig. 3 Structures of some synthetic dihydrobenzofurans.

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,<sup>24–26</sup> organocatalysis,<sup>27</sup> salt catalyzed synthesis<sup>28</sup> as well as electrochemical and photochemical synthesis.<sup>29,30</sup> Transition metal (TM)-catalyzed reactions involving the



synthesis of dihydrobenzofuran skeletons are one of the most reliable and beneficial methods.<sup>31</sup> In the past years, several synthetic researchers have designed and reported facile methodologies for the efficient synthesis of dihydrobenzofurans. In this regard, Blum<sup>32</sup> *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<sup>33</sup> in 2018. Furthermore, Henry and coworkers<sup>34</sup> in 2018 described an Fe and Cu dual catalysis protocol for the synthesis of 2,3-dihydrobenzofurans using substituted phylethan-2'-ol **22**. Ir-catalyzed synthesis of 2,3-dihydrobenzofuran was reported by Ohmura and coworkers<sup>35</sup> 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<sup>36</sup> 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<sup>37</sup> *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.<sup>38–40</sup>

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.<sup>41</sup> Several reviews regarding the synthesis of dihydrobenzofurans have been published to date. In 2019, Laurita *et al.*<sup>42</sup> published a review on the synthesis of 2,3-dihydrobenzofurans covering the data from 2012 to 2019. Similarly, Dapkekar<sup>43</sup> *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).

## 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.<sup>44</sup>

### 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.<sup>45</sup> 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.<sup>46</sup> Considering the significance of utilization of TM-mediated C–H functionalization towards the synthesis of several heterocycles, Zhang<sup>47</sup> *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  $[\text{Cp}^*\text{RhCl}_2]_2$  and NaOAc (as a base) to synthesize desired products **29** in moderate to high yields (37–80%) (Scheme 1).

In 2022, Song<sup>48</sup> *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

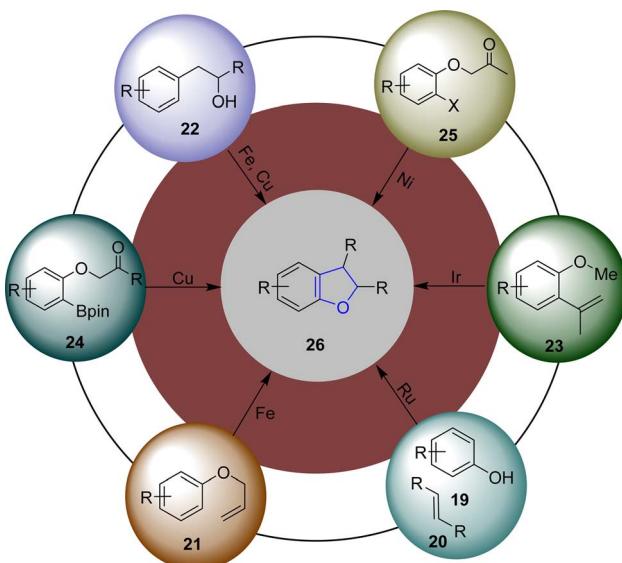
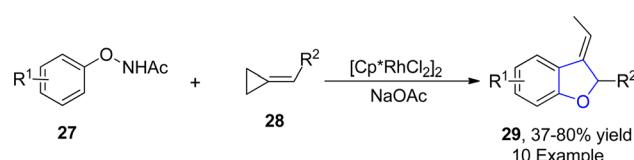


Fig. 4 Different transition metal-induced synthetic routes for the synthesis of dihydrobenzofuran derivatives.



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



phenoxyacetamides **31** were made to react with diazoxyindoles **30** in the presence of the rhodium-based catalyst ( $\text{RhCp}^*\text{Cl}$ ), 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.

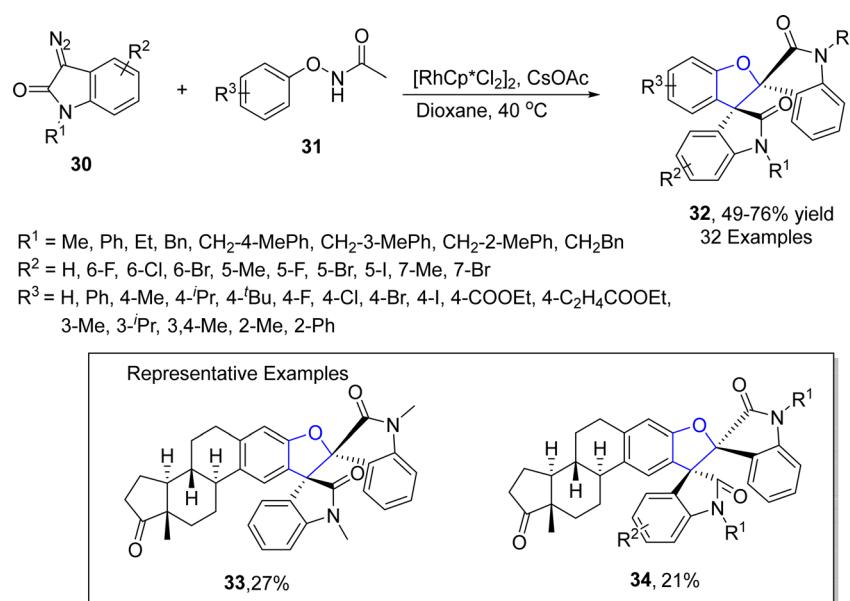
Sun<sup>49</sup> *et al.* in 2022 envisioned another rhodium-catalyzed difunctionalization of *p*-substituted olefinic arenes **35** to synthesize 2,3-dihydrobenzofuran derivatives **39**, **40** and **41**. Olefinic arenes **35** were made to react with unsaturated reagents such as isocyanates **38**, 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<sup>50</sup> *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 ( $\text{Zn}(\text{OAc})_2$ ) 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).

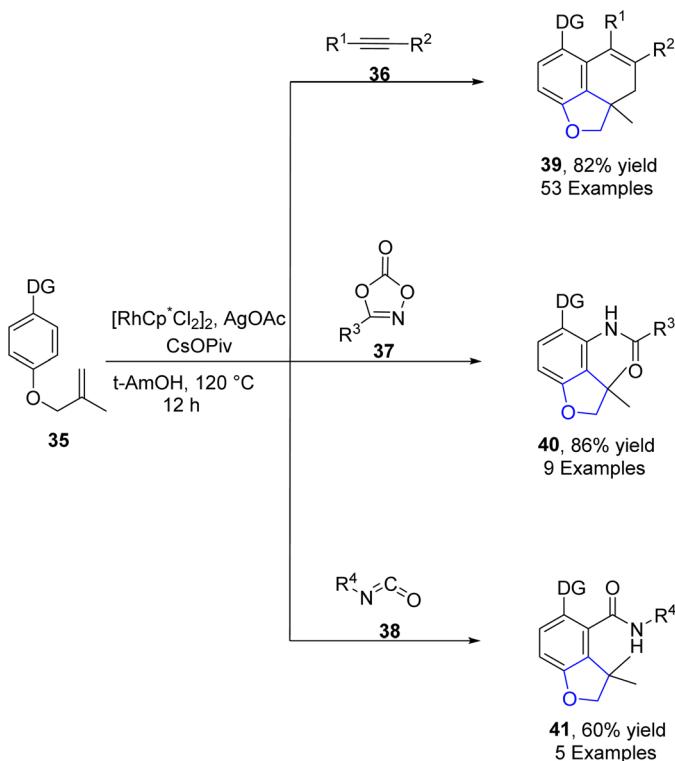
In the same year, another rhodium-catalyzed approach for the asymmetric synthesis of dihydrobenzofuran derivatives **51** was put forward by Yu<sup>51</sup> *et al.* In their methodology, aryl-joined alkenes **49** and substituted dioxazolone **37** were subjected to chiral rhodium-promoted carboamidation, using copper acetate as an additive in the presence of  $\text{AgSbF}_6$  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<sup>52</sup> *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  $[\text{RhCp}^*\text{Cl}_2]_2$  catalyst, employing cesium acetate as a base in methanol : water (2 : 1) solvent. As a consequence, imidazole-containing 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**.





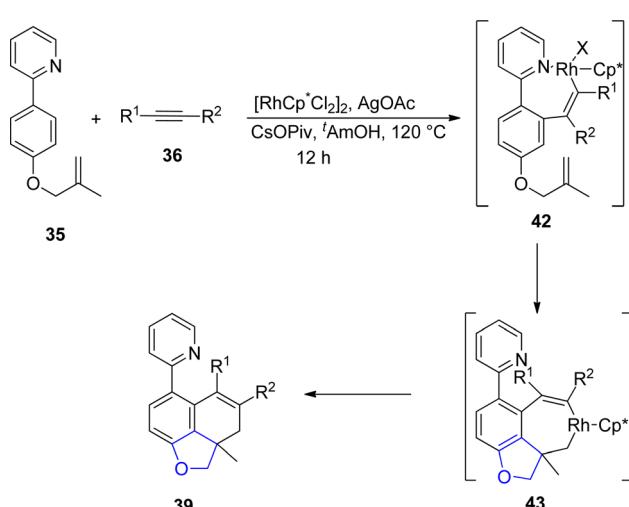
$\text{DG} = 5\text{-MePy, 5-OMePy, 5-FPy, 5-ClPy, 5-CF}_3, 4\text{-MePy, 4-OMePy, 4-FPy, 4-ClPh, fused PhPy, pyridine}$   
 $\text{R}^1 = 4\text{-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 4-}^t\text{BuPh, 4-CF}_3, 4\text{-CO}_2\text{EtPh, 4-CNPh, 3-MePh, 3-OMePh, 4-FPh, 3-ClPh, 3-BrPh, 3-CO}_2\text{EtPh, Ph, (Me)}_2\text{Ph, 2-Naph, 2-furan, 2-thiophene, C}_2\text{H}_4\text{OTIPS, Me, Et, }n\text{-Pr, C}_2\text{H}_4\text{OMe, CH}_2\text{OMe}$   
 $\text{R}^2 = 4\text{-MePh, 4-OMePh, 4-FPh, 4-ClPh, 4-BrPh, 4-}^t\text{BuPh, 4-CF}_3, 4\text{-CO}_2\text{EtPh, 4-CNPh, 3-MePh, 3-OMePh, 4-FPh, 3-ClPh, 3-BrPh, 3-CO}_2\text{EtPh, Ph, (Me)}_2\text{Ph, 2-Naph, 2-furan, 2-thiophene,}$   
 $\text{R}^3 = \text{PhCH}_3, \text{PhOCH}_3, \text{Ph, Ph}^t\text{Bu, Naph}$   
 $\text{R}^4 = \text{PhOCH}_3, \text{PhCH}_3, \text{PhF, PhCl}$

Scheme 3 Synthesis of diverse dihydrobenzofuran derivatives 39–41.

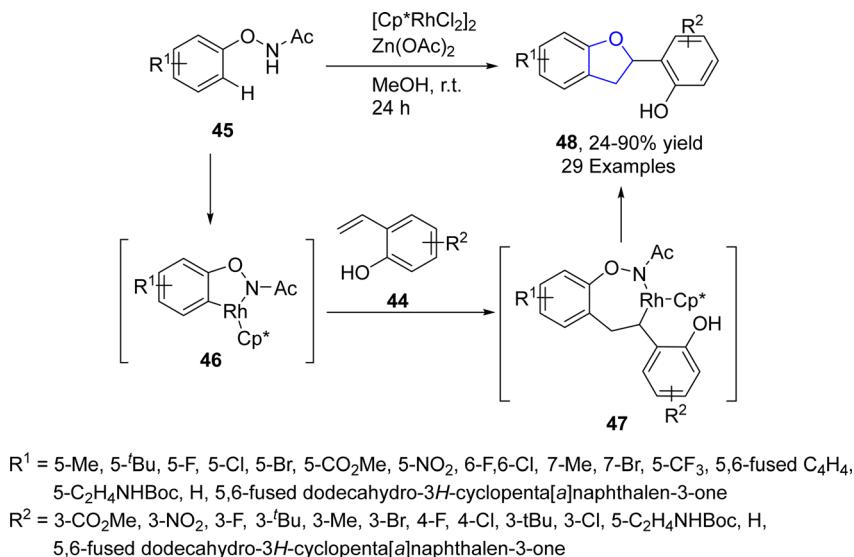
the activation of the C–H bond to generate rhodacycle intermediates 53 & 53\*. The rhodacycle intermediate 53 was then supposed to undergo migratory insertion to generate the seven-

membered intermediate 54, which underwent contraction to furnish the target molecules 55 (Scheme 7).

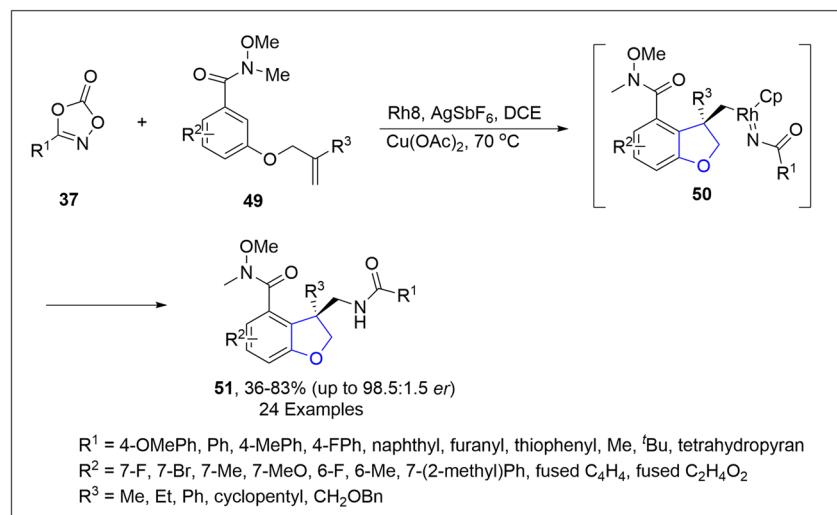
Oxa-Michael addition reaction is one of the significant reactions of Michael addition for the construction of C–O skeletons and is used for several methodological approaches towards dihydrobenzofurans synthesis.<sup>53</sup> In this regard, Zhu<sup>54</sup> *et al.* in 2021 accomplished the synthesis of diverse stereoisomers of asymmetric 2,3-dihydrobenzofurans 58, 59, 60 and 61 *via* one pot, stereodivergent dual catalysis. In their novel methodology, arylvinyl diazoacetates 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.



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



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



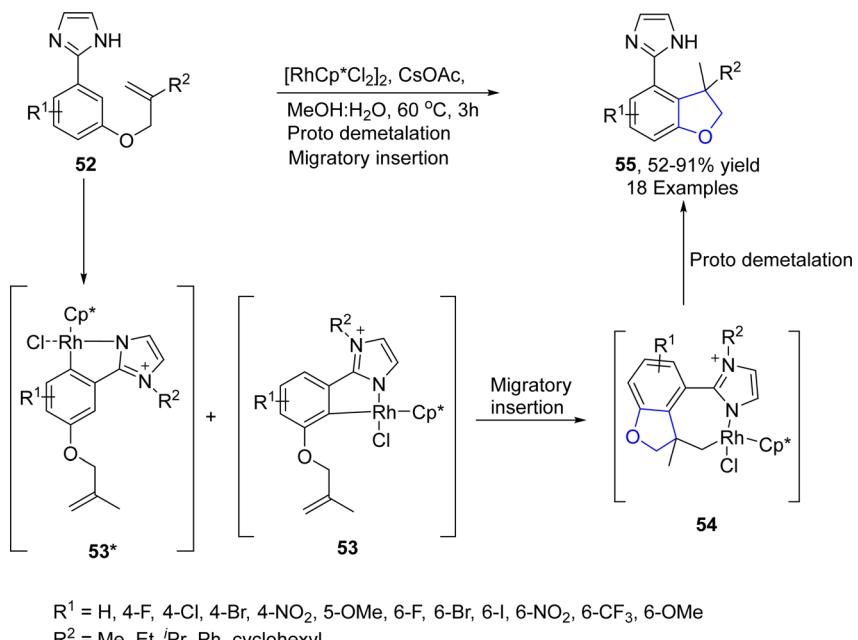
Scheme 6 Asymmetric synthesis of 2,3-dihydro-3-benzofuranmethanamides 51.

Metal carbenes are diverse intermediates that enable particular C–C bond forming transformations including C–H insertion,<sup>55</sup> ylide formation,<sup>56</sup> and aromatic addition reactions.<sup>57</sup> The asymmetric synthesis of 2,3-dihydrobenzofurans involving the insertion of carbene precursors into C(sp<sup>3</sup>)–H bonds potentially provides access to various crucial compounds like dihydrobenzofurans.<sup>58</sup> In this regard, in 2021, Bi<sup>59</sup> *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  $\alpha$ -C(sp<sup>3</sup>)–H bond of ether (Scheme 9). This efficient protocol was also used for the

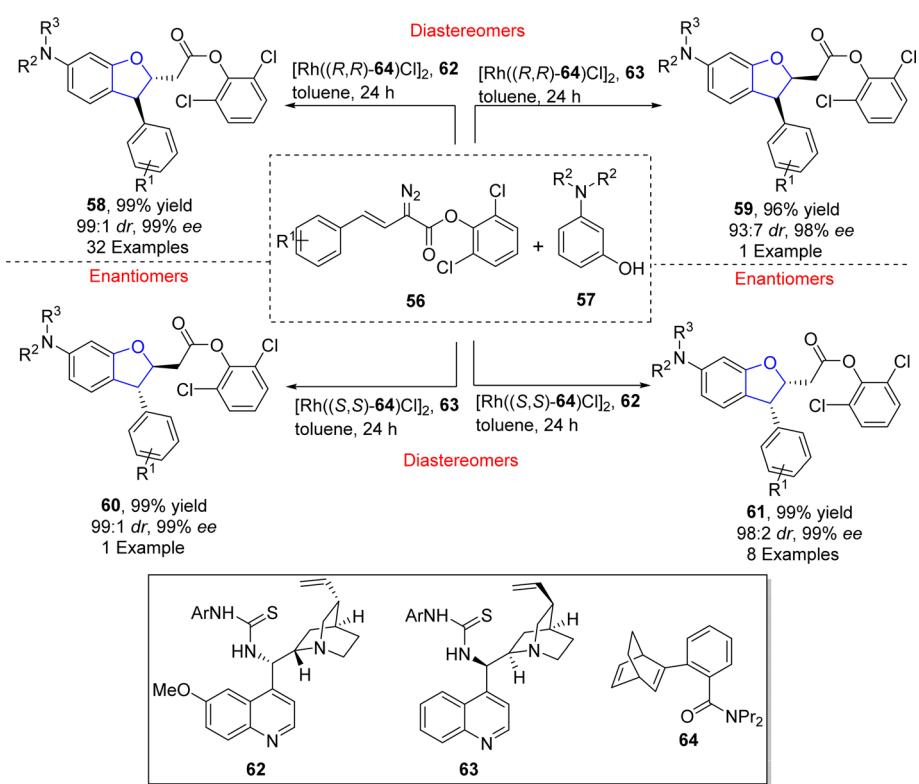
gram-scale synthesis of diverse 2,3-dihydrobenzofuran derivatives. Bi and coworkers also synthesized various enantioselective natural and bioactive molecules **67**, **68**, **69** and **70** employing the above methodology (Fig. 5).

Buckley<sup>60</sup> *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 aryl diazoacetates **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<sup>61</sup> *et al.* accomplished the Rh and asymmetric phosphoric acid **79** catalyzed synthesis of 2,3-dihydrobenzofurans **78** *via* stereoselective Mannich type



Scheme 7 Synthesis of imidazole-containing dihydrobenzofuran derivatives 55



R<sup>1</sup> = 2-F, 3-OMe, 3-Me, 3-Br, 4-OMe, 4-Me, 4-Cl, 4-CF<sub>3</sub>, 3,4-OMe, 3,5-diOMe, 3,4,5-triOMe, 3,4-fused C<sub>4</sub>H<sub>4</sub>, H, furanyl, thiophenyl

$R^2 = R^3 = \text{Me, Et, } Bn, \text{ piperidine, pyrrolidine, morpholine, 1-benzylpiperazine, 1-benzylpyrrolidine, 1-(benzyloxy)piperidine, azepane}$

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

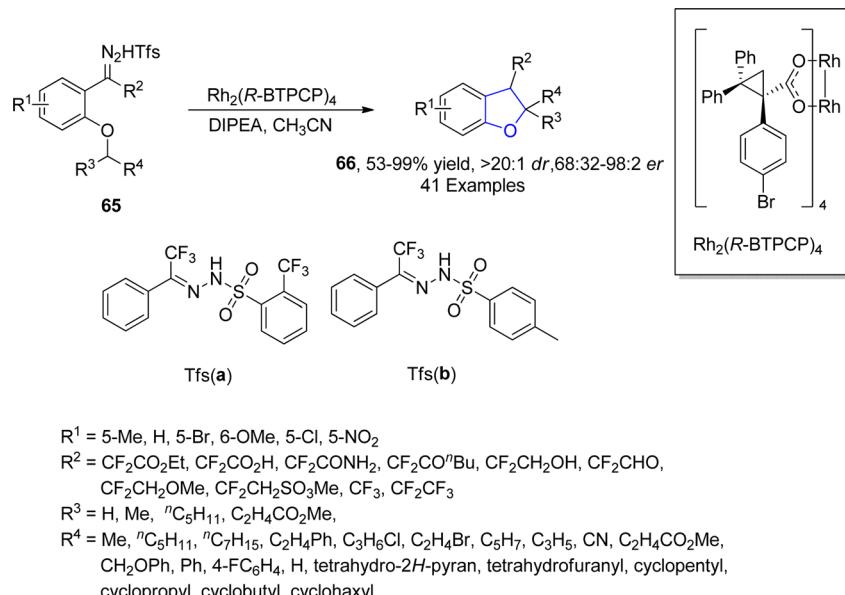
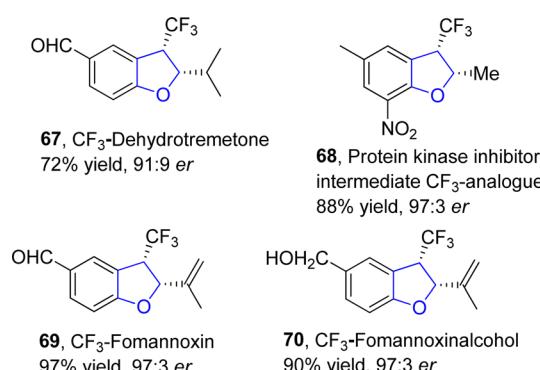
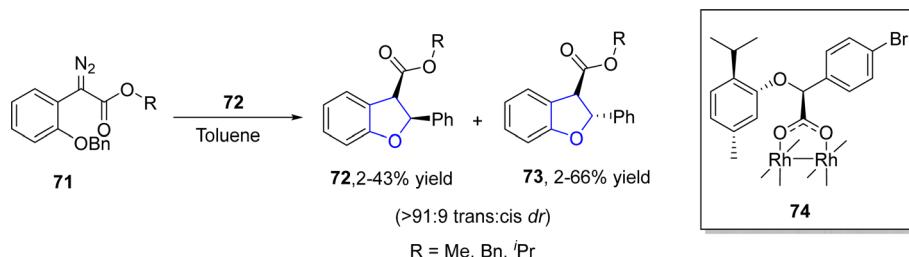
Scheme 9 Synthesis of asymmetric fluoroalkyl dihydrobenzofurans **66**.

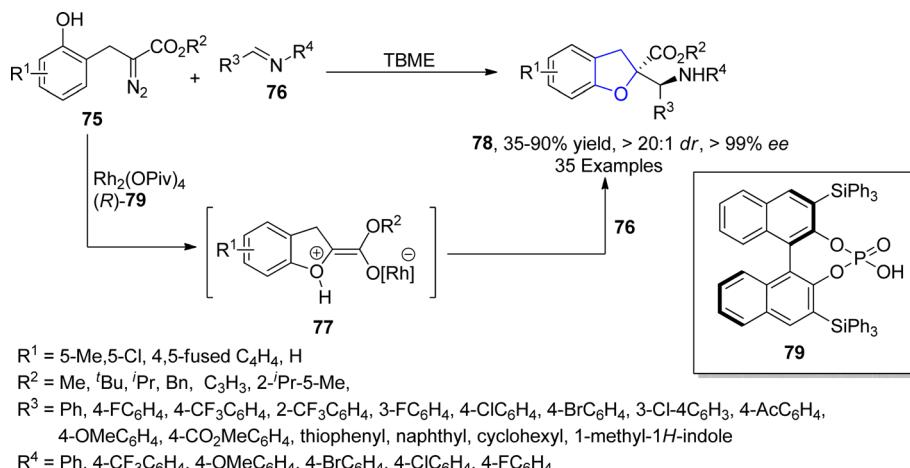
Fig. 5 Synthesized natural and bioactive molecules.

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,

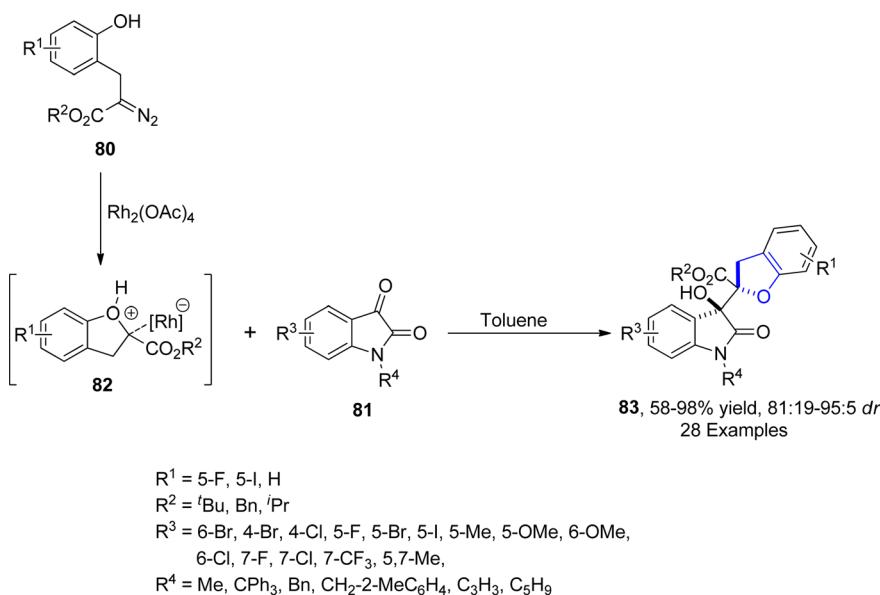
followed by the interception of **77** with imines **76** to generate Mannich-type products **78** in the presence of chiral phosphoric acid **77** (Scheme 11). Further transformations of the synthesized compounds were also carried out to demonstrate the synthetic efficacy of the mentioned approach.

In 2022, Hu<sup>62</sup> *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  $\mu$ M and 14.48  $\mu$ M IC<sub>50</sub> values, respectively (Fig. 6). In order to demonstrate the practicality of the synthetic strategy, several spiro heterocyclic and amide products were

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



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



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

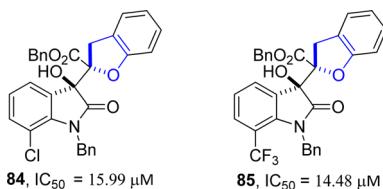
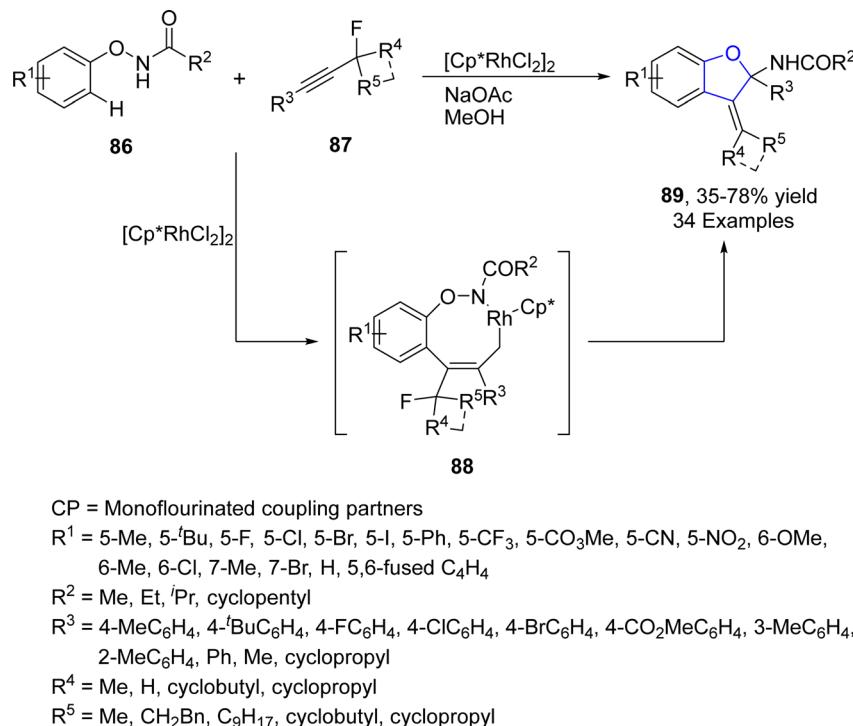


Fig. 6 Structures of compounds **84** & **85** exhibiting anticancer potential.

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<sup>63</sup> *et al.* in 2021 demonstrated the synthesis of  $\alpha$ -

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 [ $\text{Cp}^*\text{RhCl}_2$ ]<sub>2</sub> 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.



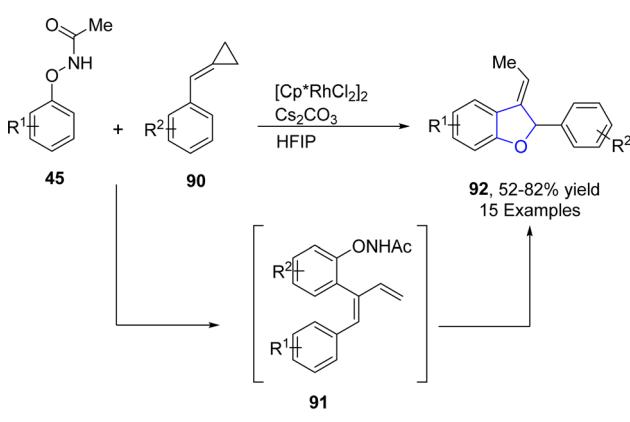
Scheme 13 Synthesis of 3-alkylidene-2,3-dihydrobenzofurans 89.

Singh<sup>64</sup> *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.<sup>65</sup> 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  $\beta$ -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.

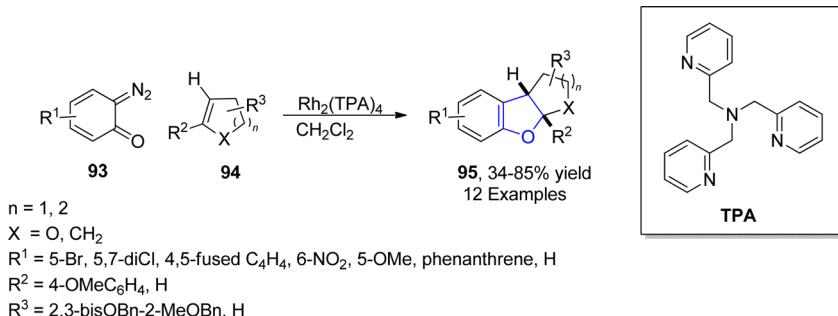
In 2021, Paymode and Sharma<sup>66</sup> designed a facile approach for the preparation of polycyclic 2,3-dihydrobenzofuran derivatives 95 *via* a rhodium-catalyzed system. In their synthetic approach, diazo compounds 93 were condensed with 2,3-dihydrofurans/cyclopentenes/cyclohexenes 94 *via* the [3 + 2] annulation process in the presence of Rh<sub>2</sub>(TPA)<sub>4</sub> 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.<sup>67</sup> Employing the mentioned methodology, Paymode and Sharma also performed the total synthesis of naturally occurring aflatoxin B<sub>2</sub> 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.<sup>68</sup> Jiang<sup>69</sup> *et al.* in 2022 carried out the rhodium-mediated one pot synthesis of benzofuran-3(2H)-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 14 Synthesis of 3-ethylidenedihydrobenzofuran derivatives 92.





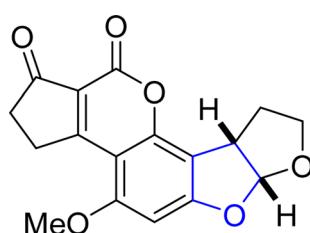
Scheme 15 Synthesis of fused rings containing 2,3-dihydrobenzofuran derivative 95.

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 salicyclaldehydes **97**, followed by ligand exchange with aryl cyclopropanols **98**,  $\beta$ -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  $\beta$ -hydride elimination and oxy-Michael addition to give benzofuranones **100**. Substituted

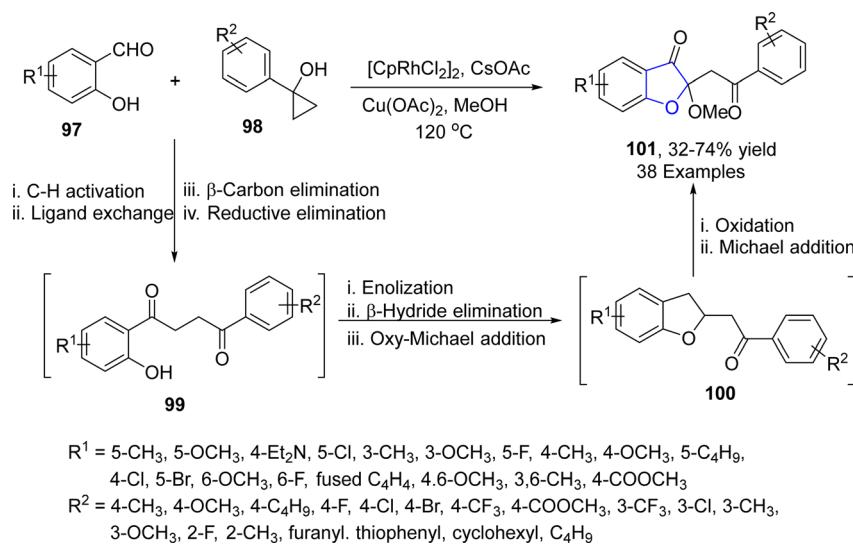
benzofuranones **100** were then assumed to be reoxidized, followed by methanol involving Michael addition to afford target molecules **101** (Scheme 16).

## 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.<sup>70</sup> 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.<sup>71</sup> 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.<sup>72</sup> In 2021, Wu<sup>73</sup> *et al.* disclosed an enantioselective,



96a, Antimicrobial

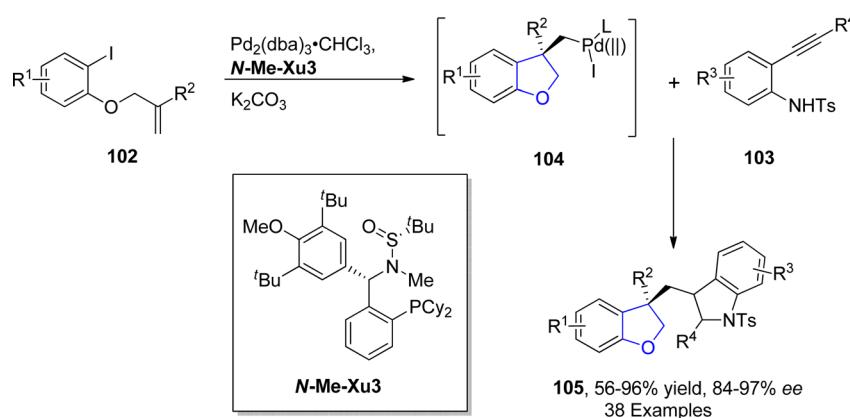
Fig. 7 Structure of aflatoxin B<sub>2</sub> 96a.

Scheme 16 Synthesis of benzofuran-3(2H)-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  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  along with ligand *N*-Me-Xu<sub>3</sub> *via* Heck/Cacchi reactions to achieve dihydrobenzofurans in excellent yields (84–97%). Asymmetric  $\sigma$ -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 enantioselective excess (84–97% ee) (Scheme 17). The gram scale synthesis

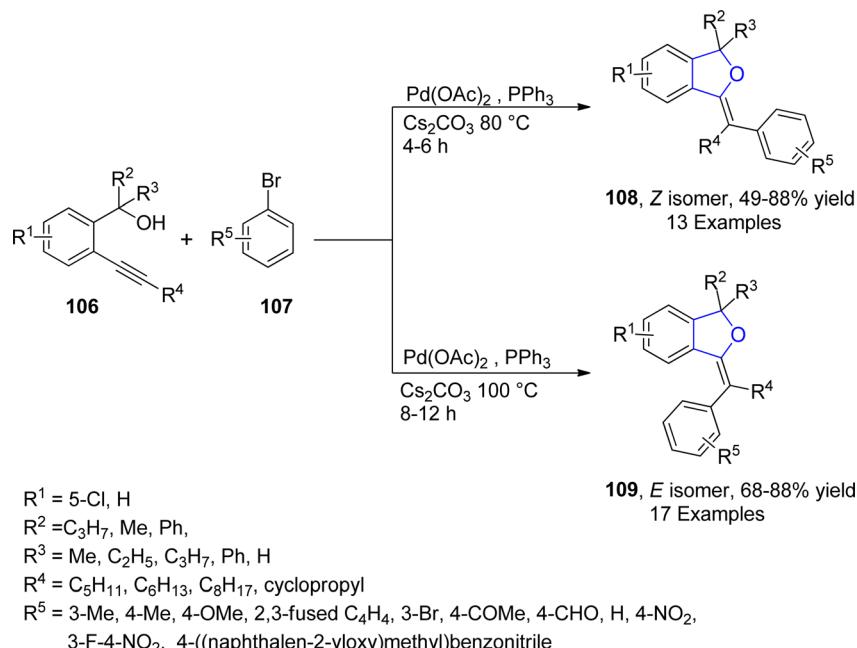
was also demonstrated along with the derivatization of the synthesized compounds.

In 2021, Sreenivasulu and Satyanarayana<sup>74</sup> 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).



$\text{R}^1$  = 5-Me, 5-Ph, 5- $t$ Bu, 5-C(Me)<sub>2</sub>Ph, 5-F, 5-Cl, 5-Br, 5-NO<sub>2</sub>, 5-CF<sub>3</sub>, H, piperidin-1-yl methanone  
 $\text{R}^2$  = C<sub>5</sub>H<sub>11</sub>, C<sub>2</sub>H<sub>4</sub>Ph,  $t$ Pr,  $t$ Bu, C<sub>3</sub>H<sub>6</sub>-3-Me-1H-indole, CH<sub>2</sub>TMS, Me, C<sub>3</sub>H<sub>6</sub>-benzo[*d*][1,3]dioxol-4-ol, C<sub>3</sub>H<sub>6</sub>-4,4-dimethylpiperidine-2,6-dione, C<sub>3</sub>H<sub>6</sub>-oxazolidin-2-one  
 $\text{R}^3$  = 5-OMe, 5-Me, 5-CN, 5-CF<sub>3</sub>, 5-F, 5-Cl, 6-CO<sub>2</sub>Me, H  
 $\text{R}^4$  = Ph, 4-OMeC<sub>6</sub>H<sub>4</sub>, 4- $t$ BuC<sub>6</sub>H<sub>4</sub>, 4-PhC<sub>6</sub>H<sub>4</sub>, 4-CO<sub>2</sub>MeC<sub>6</sub>H<sub>4</sub>, 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 3-OMeC<sub>6</sub>H<sub>4</sub>, PMP, C<sub>3</sub>H<sub>6</sub>Cl,  $t$ Bu, cyclohexyl, thiophene

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



$\text{R}^1$  = 5-Cl, H  
 $\text{R}^2$  = C<sub>3</sub>H<sub>7</sub>, Me, Ph,  
 $\text{R}^3$  = Me, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, Ph, H  
 $\text{R}^4$  = C<sub>5</sub>H<sub>11</sub>, C<sub>6</sub>H<sub>13</sub>, C<sub>8</sub>H<sub>17</sub>, cyclopropyl  
 $\text{R}^5$  = 3-Me, 4-Me, 4-OMe, 2,3-fused C<sub>4</sub>H<sub>4</sub>, 3-Br, 4-COMe, 4-CHO, H, 4-NO<sub>2</sub>, 3-F-4-NO<sub>2</sub>, 4-((naphthalen-2-yloxy)methyl)benzonitrile

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



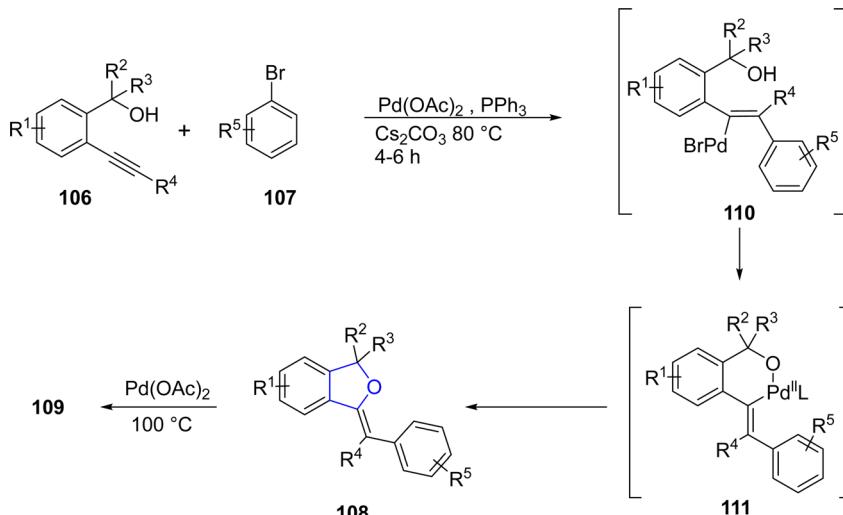
Initially, Pd-assisted intermolecular Heck coupling reaction between **106** and **107** took place to generate an intermediate **110**, followed by the elimination reaction to form a palladacycle **111**. Further, this palladacycle underwent intramolecular *oxo*-cyclization to furnish the desired heterocyclic 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.<sup>75</sup> Taking into consideration the wide synthetic utility of borylated compounds, Wu<sup>76</sup> *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  $B_2\text{Pin}_2$  **112** in the presence of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  catalyst exploiting *N*-Me–Xu<sub>3</sub> 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

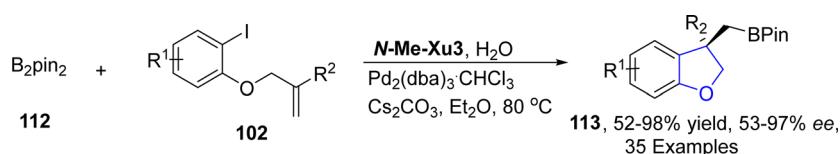
accomplishment of chromane, indoline and indane boronic esters (Scheme 20).

In 2022, Guo<sup>77</sup> *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  $\alpha,\beta$ -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  $\text{Pd}(\text{PhCN})_2\text{Cl}_2$  was subjected as a catalyst along with *Cy*<sub>2</sub>NMe (base) in MeCN (solvent) (Scheme 21). The reaction mechanism was proposed to proceed *via* the reaction of reduced Pd species [ $\text{Pd}(0)$ ] 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.<sup>78</sup> Marchese<sup>79</sup> *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**.

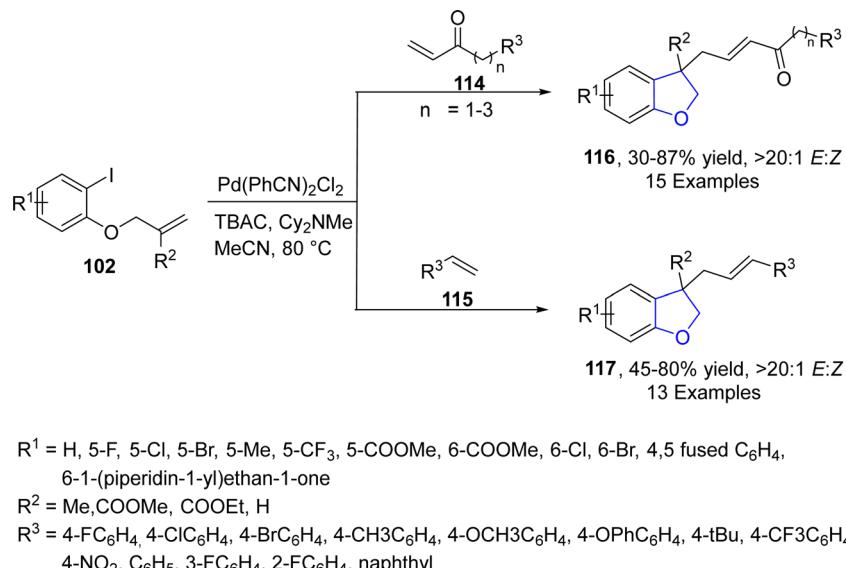


$R^1 = 5\text{-Me, 5-Ph, 6-}^t\text{Bu, fused C}_4\text{H}_4, \text{fused C}_2\text{H}_2\text{NSO}_2\text{Ph, 5-cumene, 5-F, 5-Cl}$

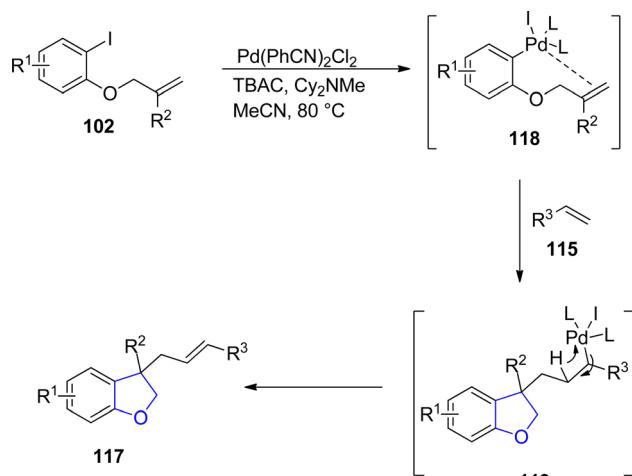
$R^2 = \text{Me, Et, }^n\text{Pr, }^n\text{Bu, }^i\text{Pr, }^t\text{Bu, Bn, 4-MePh, 4-FPh, 4-ClPh, 4-CF}_3\text{Ph, 3-FPh,}$   
 $3\text{-CIPh, 3-NO}_2\text{Ph, 3-MePh, 3-MeOPh, 3-}^t\text{BuPh, 2-MePh, 3,5-FPh, 3,4,5-FPh,}$   
 $\text{naphthyl, CH}_2\text{-dibenzo[b,d]thiophene, CH}_2\text{TMS, (CH}_2\text{)}_4\text{Cl, (CH}_2\text{)}_4\text{-isoindoline}$   
 $\text{-1,3-dione, CH}_2\text{-3-methyl-1H-indole, Ph}$

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





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.

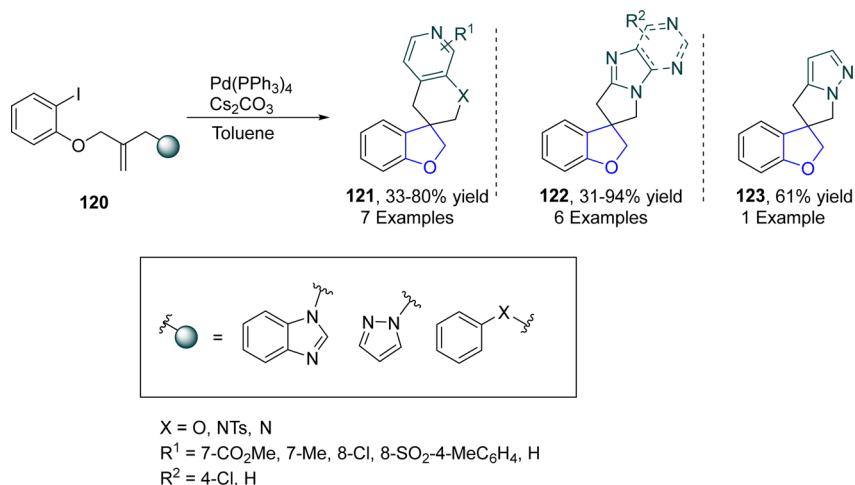
compounds 121, 122 and 123 *via* palladium catalysis. In their synthetic approach, *o*-substituted aryl iodides 120 were transformed into corresponding bis-heterocyclic spirocycles 121, 122 and 123 by following the Mizoroki-Heck-type reaction pathway in the presence of  $Cs_2CO_3$  (used as base). Initially, 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<sup>80</sup> *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

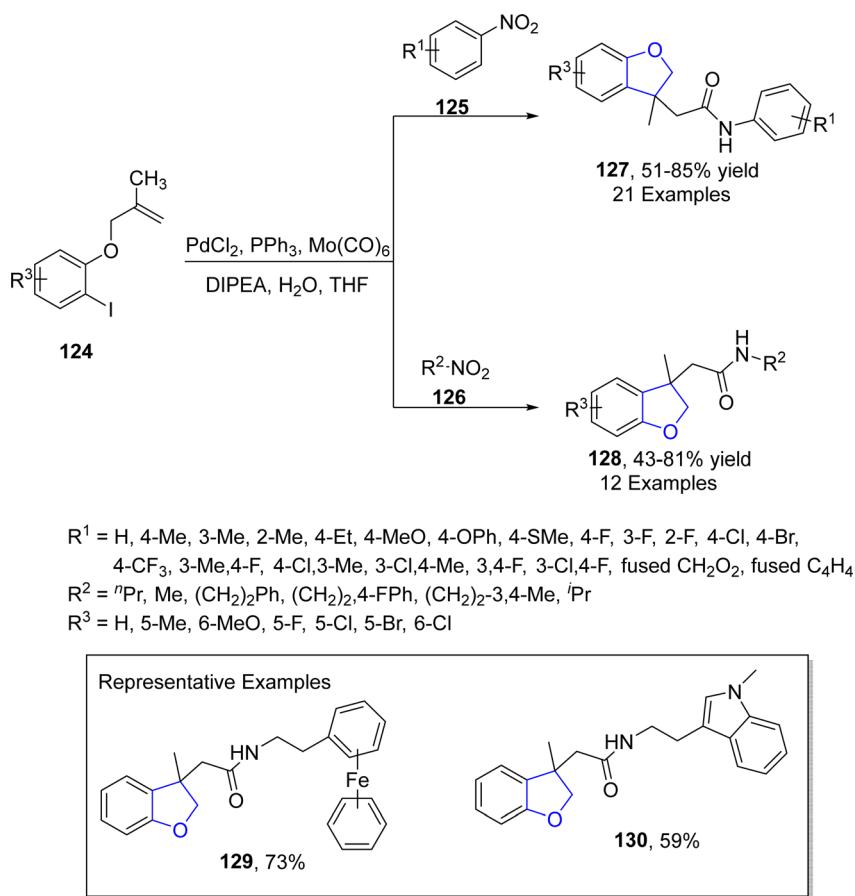
utilizing  $PdCl_2$  as a catalyst,  $Mo(CO)_6$  for the release of CO, triphenylphosphine as the ligand, DIPEA as base in tetrahydrofuran solvent without any addition of additive and reducing agent (Scheme 24). The synthetic pathway was proposed to follow the certain steps, *i.e.*, oxidative addition, 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.<sup>81</sup> 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.<sup>82</sup> In 2023, Ding<sup>83</sup> *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



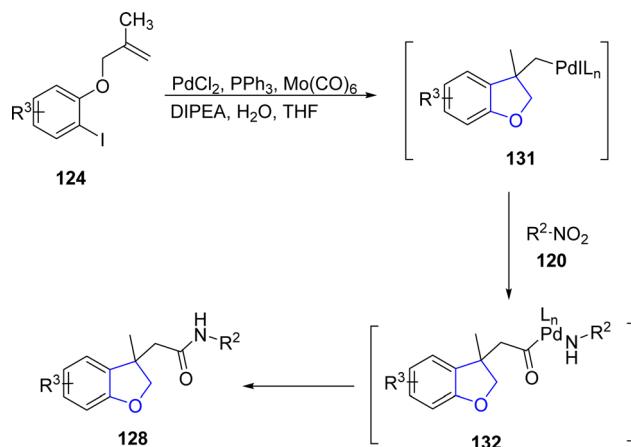
Scheme 23 Synthesis of heterocyclic spiro-2,3-dihydrobenzofurans 121, 122 and 123.



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.<sup>84</sup> In this perspective, Zhou<sup>85</sup> *et al.* in 2021 prepared



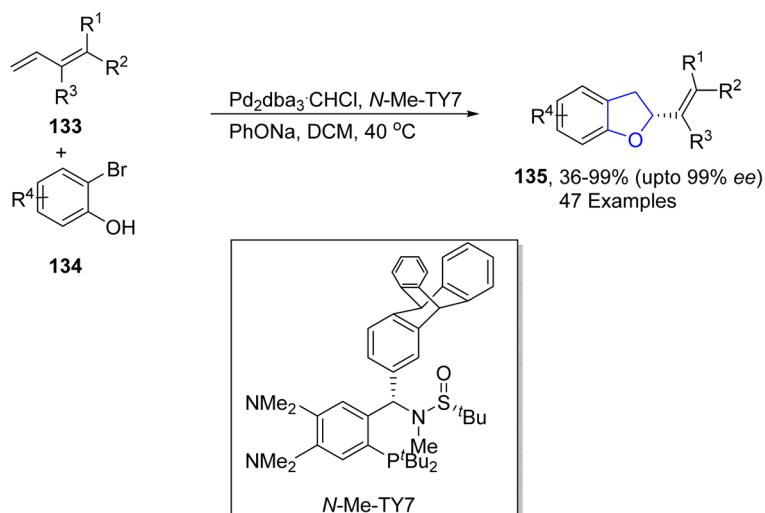
Scheme 25 Proposed mechanism for the synthesis of carbamoyl-substituted 2,3-dihydrobenzofurans 128.

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  $\text{Pd}(\text{OAc})_2$  along with  $\text{CuCl}_2$  (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<sup>86</sup> *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  $\text{NaO}^{\prime}\text{Bu}$  (as base) in a 9 : 1 ratio of PhMe and anisole (used as solvent) at 110 °C (Scheme 29).

In 2023, Sun<sup>87</sup> *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.

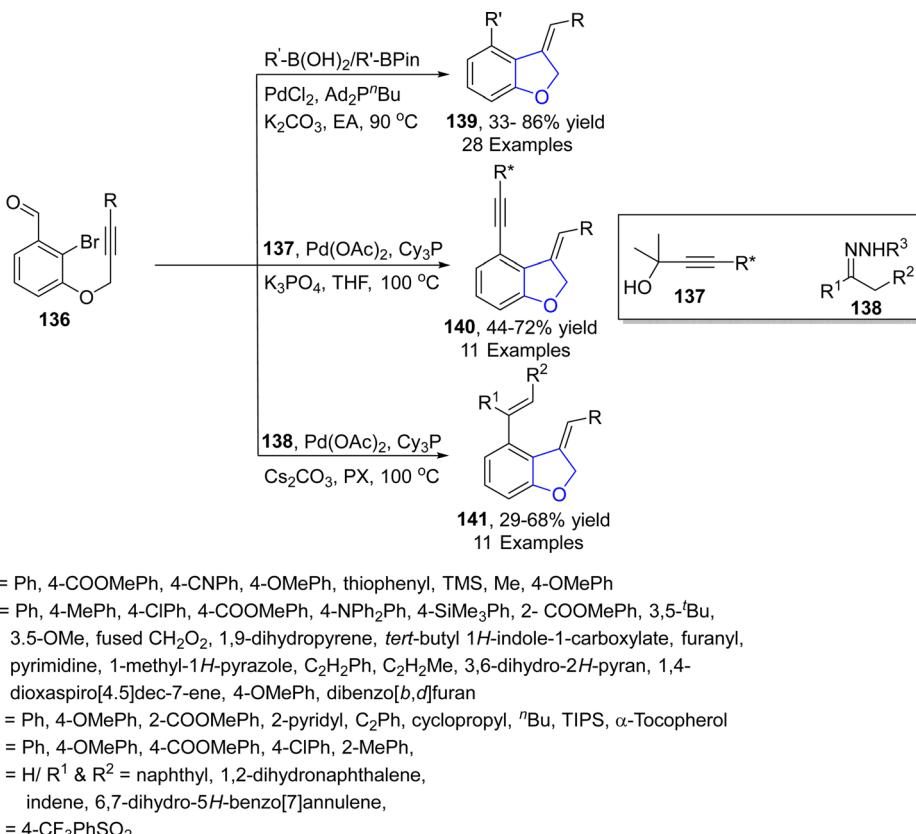
In recent times, synthesis of various heterocycles and carbocycles have been achieved by employing alkyne cyclization. In these cyclization reactions, palladium-based catalysts have gained great significance. In 2023, Sun<sup>70</sup> *et al.* reported the synthesis of dihydrobenzofurans **145** by treating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



$\text{R}^1 = \text{H, Ph, 2-MeOPh, 2-MePh, 2-CF}_3\text{Ph, 3-MePh, 3-CIPh, 4-OMePh, 4-OCF}_3\text{Ph, 4-}^{\prime}\text{BuPh, 4-PhC}_6\text{H}_4, 4\text{-CIPh, 4-CF}_3\text{Ph, 2,4,6-MePh, naphthyl, thiophenyl, cyclohexyl, C}_2\text{H}_4\text{Ph, C}_2\text{H}_2(\text{CH}_2)_{10}\text{Br, C}_2\text{H}_2\text{C}_5\text{H}_{11, C}_2\text{H}_2(\text{CH}_2)_5\text{OTBS, (R)-4,8-dimethylnona-1,7-diene, OTBS, fused C}_4\text{H}_6,$   
 $\text{R}^2 = \text{H, Me} \quad \text{R}^3 = \text{H, Me}$   
 $\text{R}^4 = \text{4-Me, 4-F, 5-OMe, 5-}^{\prime}\text{Bu, 5-Me, 5-F, 5-CF}_3, 6\text{-OMe, 6-Me, 6-F, 6-COOMe, 7-OMe, 7-Me, 7-Ac, fused C}_4\text{H}_4$

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





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<sub>2</sub>CO<sub>3</sub> as a base and tricyclohexylphosphine PCy<sub>3</sub> 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,  $\gamma$ -hydride elimination and Diels–Alder ([4 + 2] cycloaddition) reaction to furnish the spirocyclobutane-substituted dihydrobenzofurans 145 (Scheme 31).

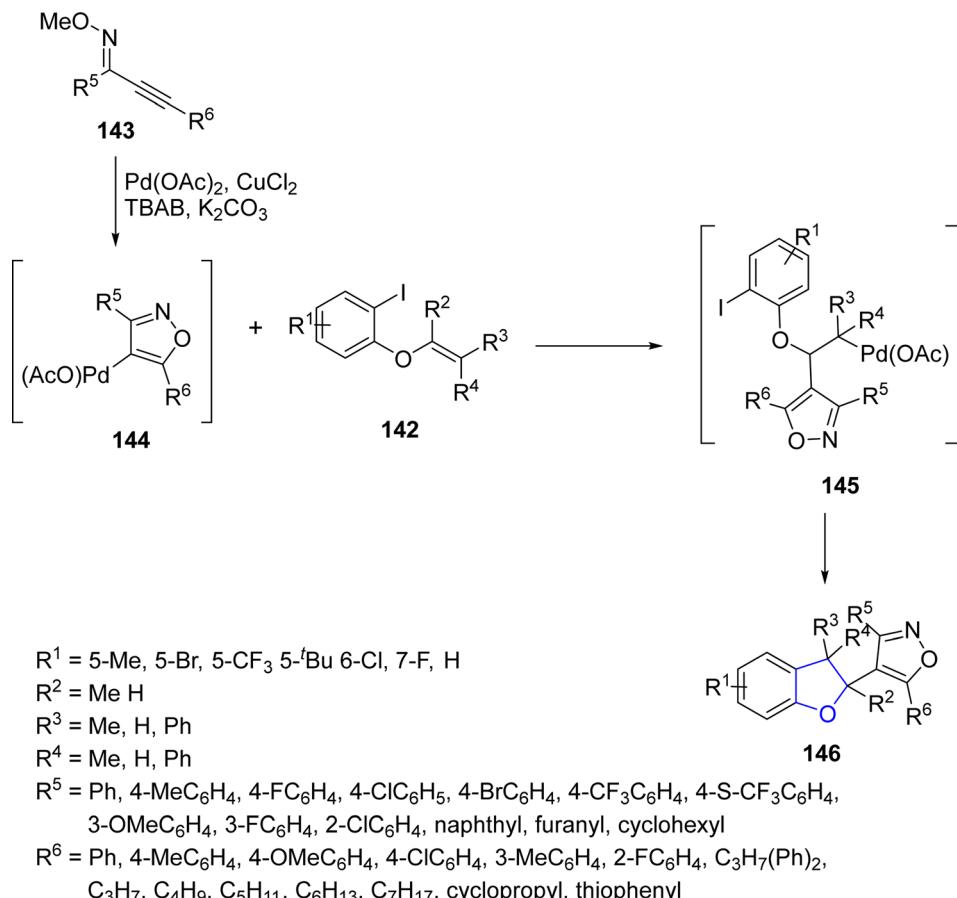
Wu<sup>88</sup> *et al.* in 2021 developed a Pd-catalyzed protocol for the synthesis of 2,3-dihydrobenzofuran derivatives 158 *via* C(sp<sup>3</sup>)-H and C(sp<sup>2</sup>)-H intramolecular coupling. In their novel methodology, alkyl phenyl ethers 156 were used as efficient starting materials, which underwent subsequent C(sp<sup>3</sup>)-H and C(sp<sup>2</sup>)-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<sup>89</sup> *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]<sub>2</sub> along with MeSO<sub>3</sub>H (used as an additive) to afford dihydrobenzofurans 162 in moderate to excellent yields (51–91%). Active Pd catalyst interacted with

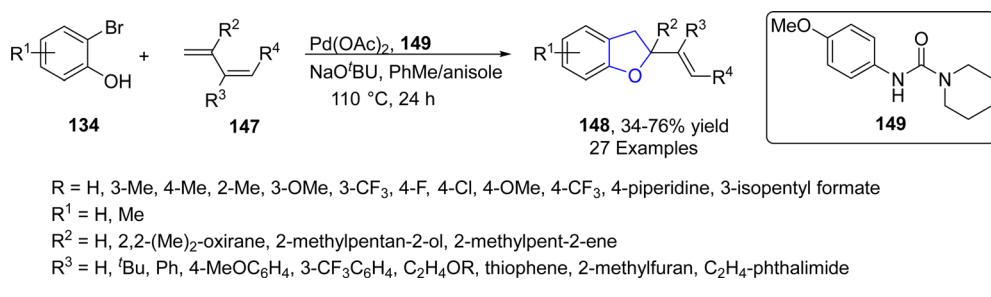
diazo compounds 160 to give carbene species, which on nucleophilic addition with 159 gave oxonium ylides that existed in equilibrium with the corresponding zwitterions 161. Zwitterions 161 were then trapped *via* Michael addition to afford desired products 162 (Scheme 33). Further, a number of substituted 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.<sup>90</sup> Cu-catalyzed synthesis also plays a crucial role in the synthesis of diverse dihydrobenzofuran scaffolds.<sup>91</sup> 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.<sup>92</sup> In this regard, Zheng<sup>93</sup> *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<sub>2</sub>CO<sub>3</sub> (used as an additive) to afford 2,3-dihydrobenzofurans 167 in low to high yields (16–85%) *via* the



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

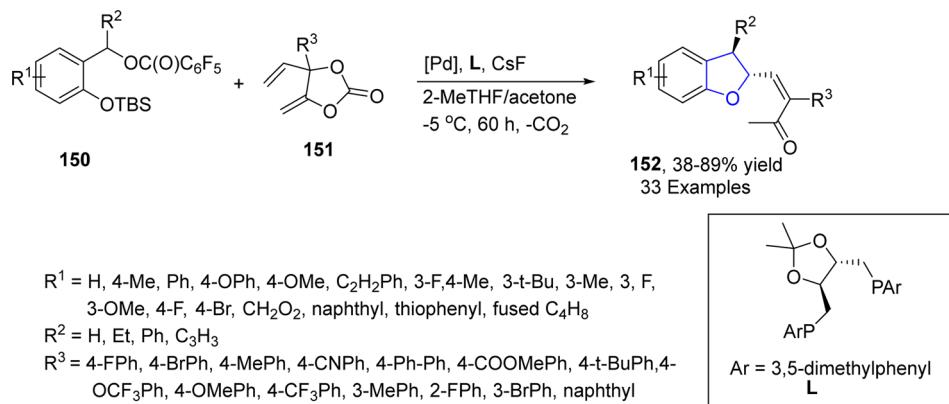


Scheme 29 Synthesis of 2,3-dihydrobenzofurans 148.

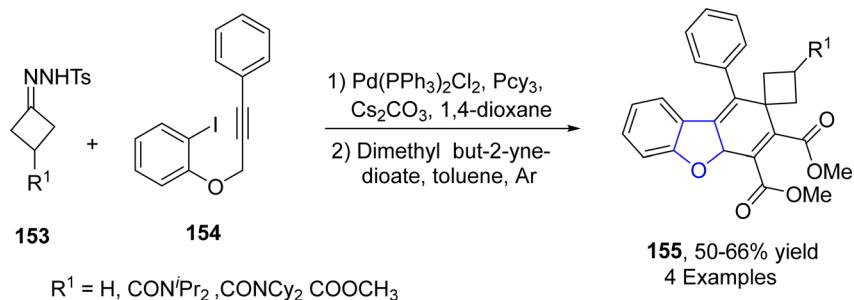
destructive insertion of 164 into 163. This synthetic methodology provides broad functional group tolerance. Cu-assisted oxime-Cu-iminyl radical was converted into  $\alpha$ -carbon radical, which underwent radical addition to give intermediate 165, followed by intramolecular addition to carbonyl group 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

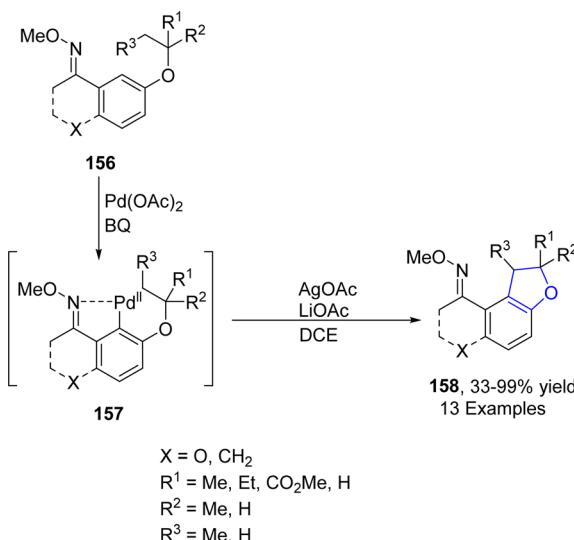
most convenient synthetic protocols for the synthesis of five-membered heterocyclic ring compounds.<sup>94</sup> Considering this, in 2021, Jing<sup>95</sup> *et al.* described the synthesis of a range of enantioselective 2,3-dihydrobenzofurans 170 *via* the Cu/SPDO-catalyzed synthetic route. In their novel approach, quinone esters 168 and substituted styrenes 169 underwent [3 + 2] cycloaddition in the presence of SPDO-ligated Cu(OTf)<sub>2</sub> 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.



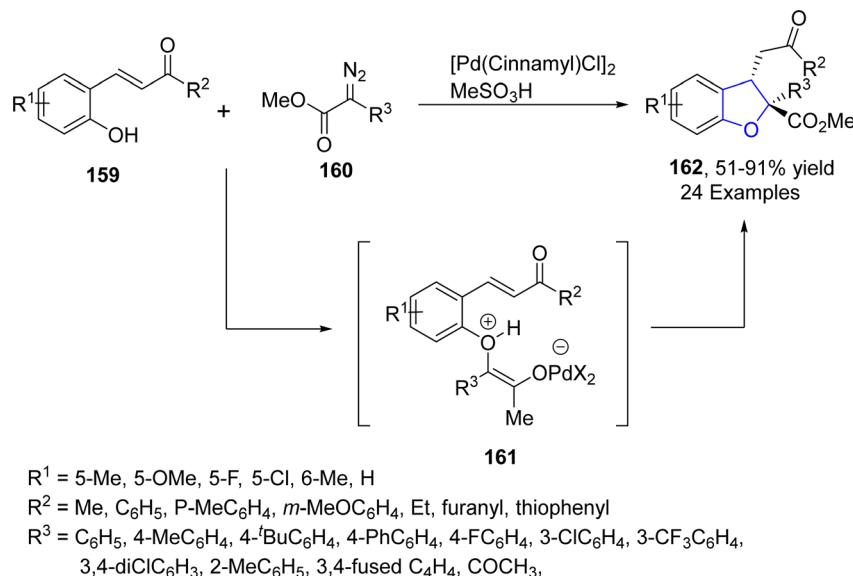
Scheme 32 Synthesis of fused cyclic dihydrobenzofurans 158.

An enantioselective and diastereoselective pathway towards the synthesis of dihydrobenzofurans 163 was given by Zhu<sup>96</sup> *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  $\text{Cu}(\text{OTf})_2$  and ligand **L** in toluene, wet tetrahydrofuran or

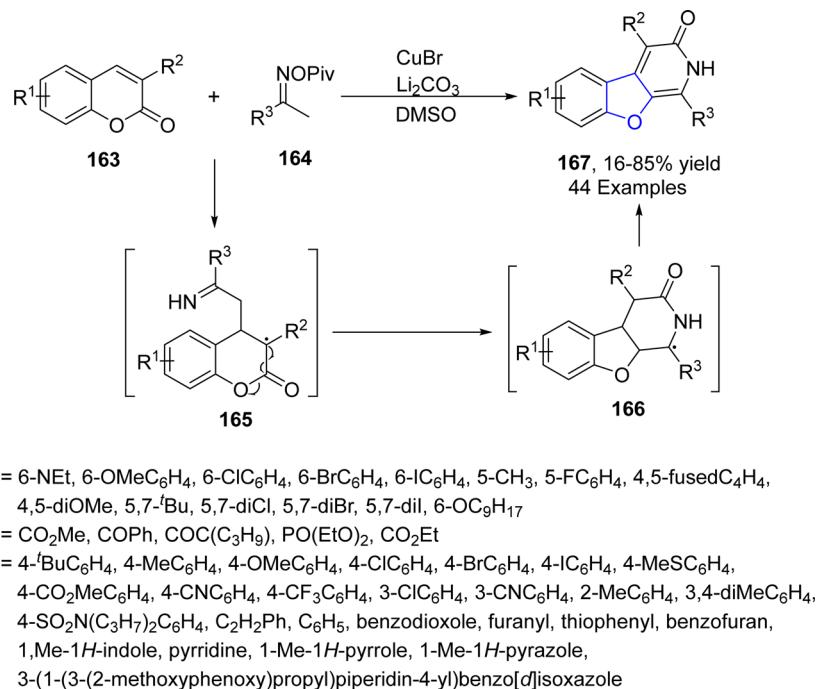
mestylene solvent, to enable the asymmetric synthesis of benzofuran derivatives 175. The reaction mechanism was suggested to move forward with the formation of intermediate 174, on the coordination of substrates and catalyst. Intermediate 174 was then believed to undergo further transformations to furnish 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<sub>2</sub> **96a** & (–)dihydroaflatoxin D<sub>2</sub> **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, anti-viral and anticarcinogenic.<sup>97</sup> In 2021, Devi *et al.*<sup>98</sup> 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<sup>99</sup> *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



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



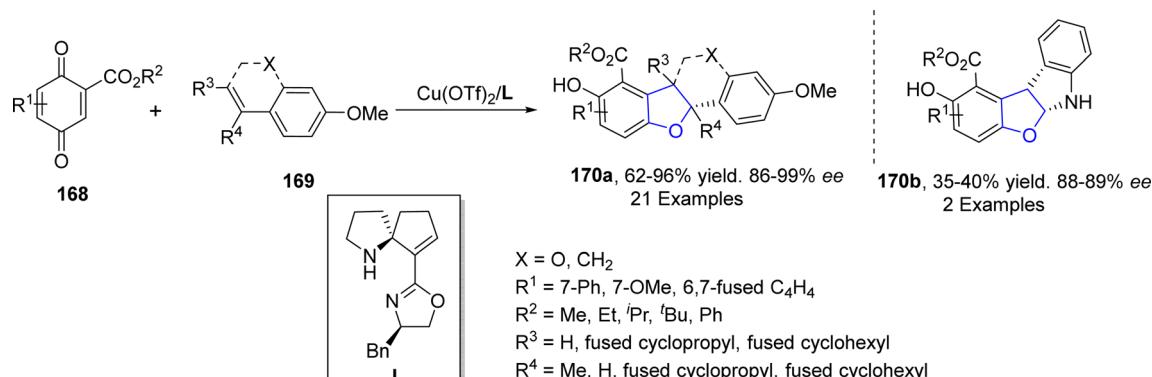
Scheme 34 Synthesis of 2,3-dihydrobenzofuran-fused pyridones 167.

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  $\pi$ -expanded system *via* double C–O cyclization. The catalytic amount of Cu(OAc)<sub>2</sub>, 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.<sup>100</sup> Cu-catalyzed intermolecular

oxidative cross coupling reactions have attracted much attention in organic synthesis to generate new dihydrobenzofuran units. In 2021, Dong<sup>101</sup> *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





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

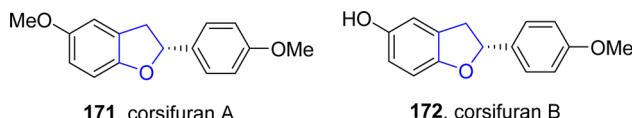


Fig. 8 Structure of asymmetric natural products 171 and 172.

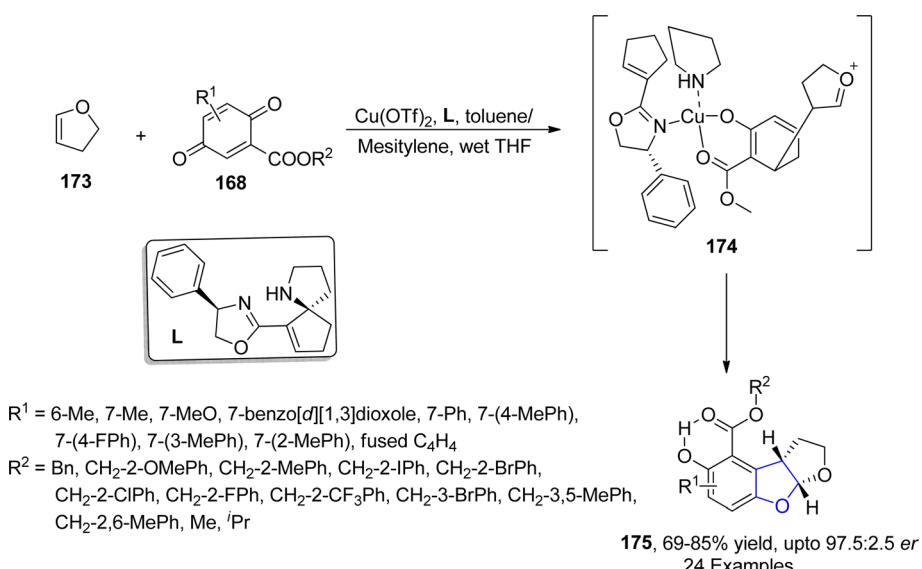
**189**, followed by the addition of -OH to **189** to afford the desired 2,3-dihydrobenzofuran skeletons **190** in excellent yields (24–95%) with notable diastereoselectivity values (>20:1 dr) (Scheme 40). Through the developed synthetic route, Licarin A **191** was also synthesized, which exhibits 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.<sup>102</sup> 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.<sup>103</sup> In reference to this, Cerveri<sup>104</sup> *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<sub>2</sub> fixation took place when *o*-aryliodines **102** were cyclized in the presence of  $[(L)Ni(H_2O)Cl]Cl$  (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<sub>2</sub> insertion to afford the target compounds in moderate to high yields (47–69%) with up to 99% enantiomeric excess (Scheme 41).

Pyranofused cyclic organic compounds are ubiquitously employed in medicinal chemistry owing to their unique



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



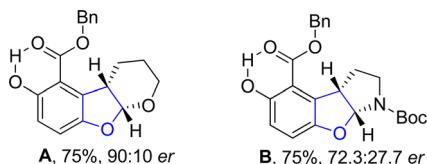


Fig. 9 Structures of olefin variant-substituted dihydrobenzofurans.

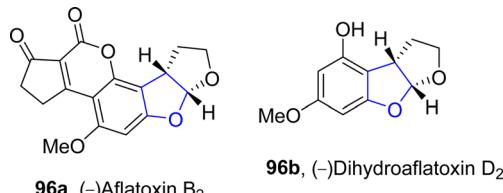


Fig. 10 Structures of naturally-occurring dihydrobenzofuran derivatives 96a and 96b.

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<sup>105</sup> *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  $\beta$ -OAc elimination and allylic rearrangement to furnish the desired dihydrobenzofurans 197 (Scheme 42).

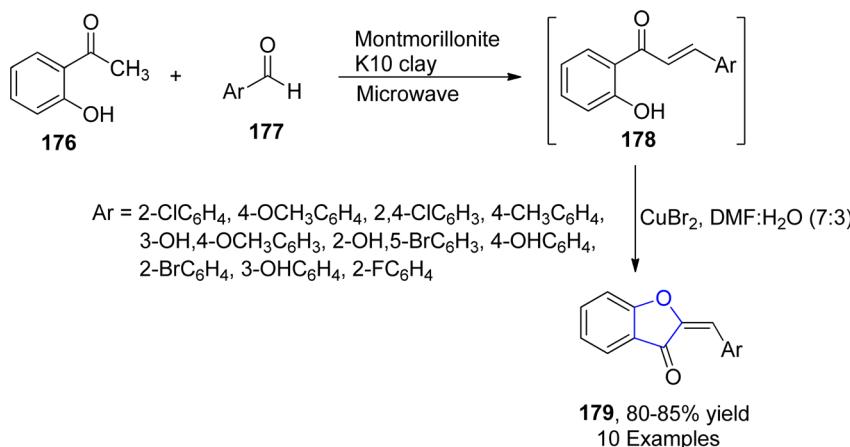
As a key component of several dicarbon-functionalization reactions, alkene aryl-acylation or aryl-carbamoylation facilitates the synthesis of structurally significant heterocycles comprising of carbonyl compounds.<sup>106</sup> In this respect, Wang<sup>107</sup> *et al.* in 2022 described a novel approach 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<sup>108</sup> *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).

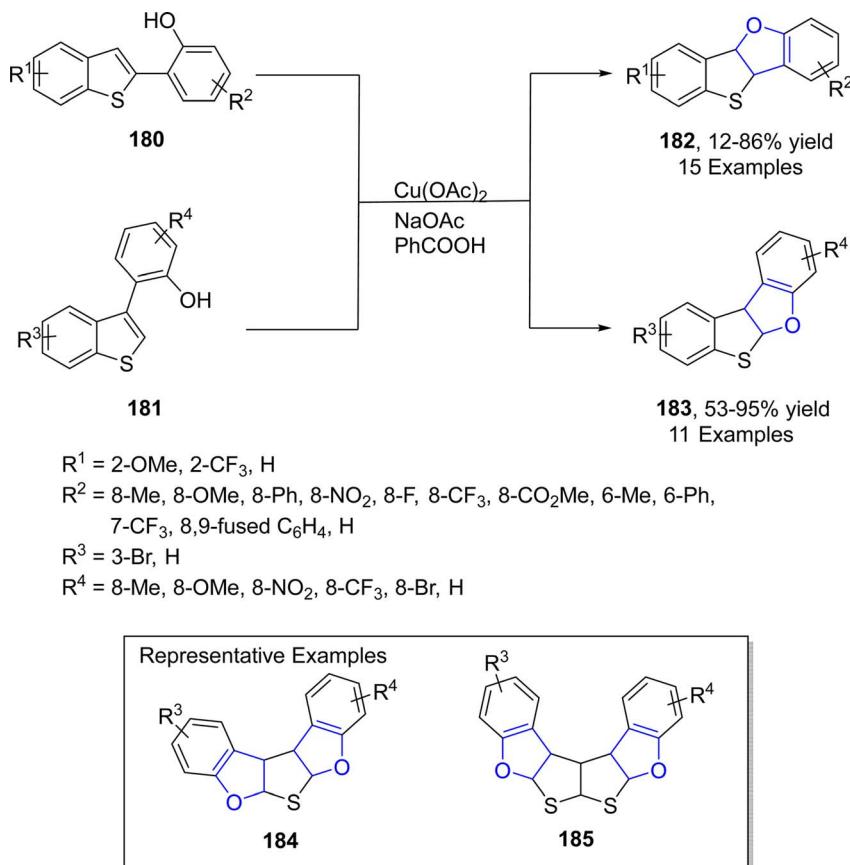
Geng<sup>109</sup> *et al.* in 2021 reported the Ni-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives 207 *via* carbonylative synthesis. In their novel methodology, *ortho*-substituted aryl iodides 124 reacted with alkyl halides 205 in the presence of Ni(acac)<sub>2</sub> (as a catalyst), 4,4'-di-*tert*-butyl-2,2'-bipyridyl (L) (as ligand), Mo(CO)<sub>6</sub> (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.<sup>110</sup> Utilizing this strategy, Déjardin<sup>111</sup> *et al.* in 2021, proposed an electro-reductive, 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

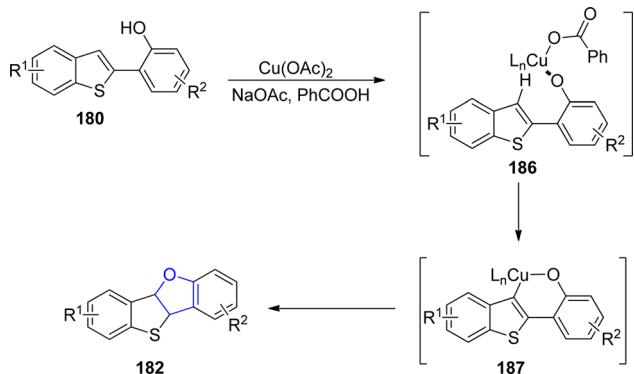


Scheme 37 Synthesis of 2-benzylidene-1-benzofuran-3-ones 179.





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



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

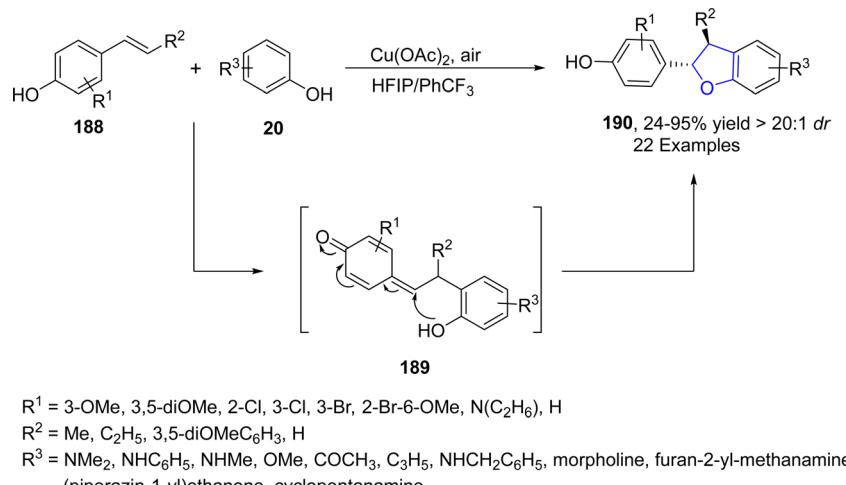
substituted 2,3-dihydrobenzofuran **211** (11–90%). The reaction was highly stereo and regio-selective. Maximum yield (90%) was observed when the reaction proceeded at 80 °C in the presence of DMF (as a solvent) (Scheme 46).

## 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<sup>112</sup> *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<sup>113</sup> *et al.* carried out the efficient synthesis of dihydrobenzofurans by involving gold-based NHC catalyst (permethylated  $\beta$ -cyclodextrin-tagged *N*-heterocyclic carbene-gold catalyst) in water. They utilized the NHC catalyst due to the hydrophobic nature of  $\beta$ -CD,<sup>114</sup> 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  $\beta$ -CD-NHC-AuCl catalyst, utilizing AgNTf<sub>2</sub> (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).



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

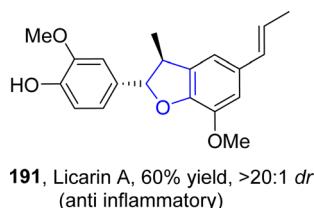
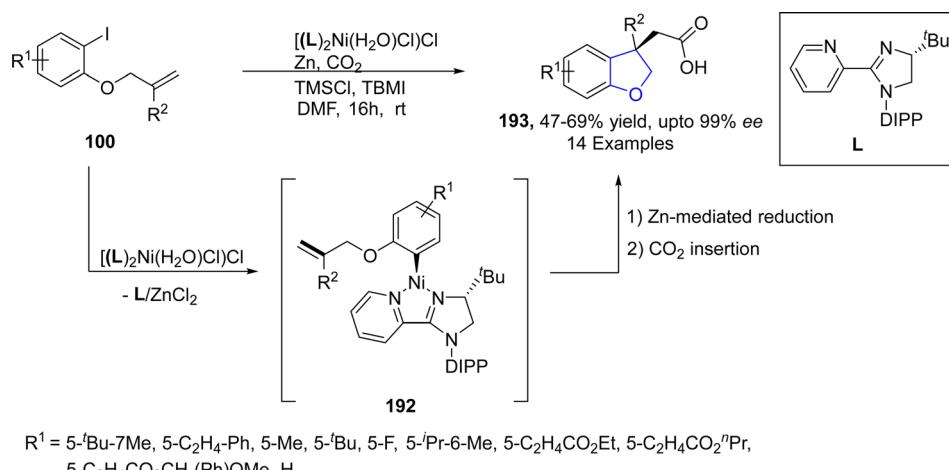


Fig. 11 Structure of licarin A 191.

Wang<sup>115</sup> *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  $\alpha$ -oxo vinyl gold carbenoid analogue. Catalytic amounts of  $^t\text{Bu-XPhosAuCl}$  (phosphine ligated aurum catalyst) and 2,6-

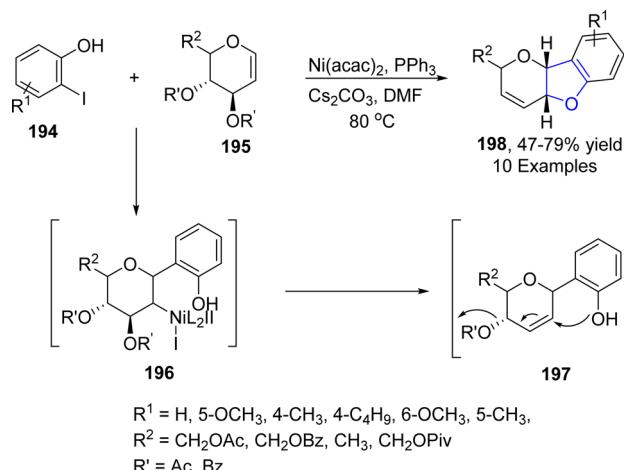
dichloropyridine *N*-oxide **222** (as an additive) were utilized in dichloroethane to achieve the desired products **221**. Gold and ligand **222** assisted 1,3-enynes **219** underwent concerted  $S_N2$  reaction and proto-deauration upon the addition of substituted phenols **20** to generate intermediate **220**. The intermediate **220** was converted to the final product **221** *via* oxa-Michael addition (Scheme 49).

Du<sup>116</sup> *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



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).

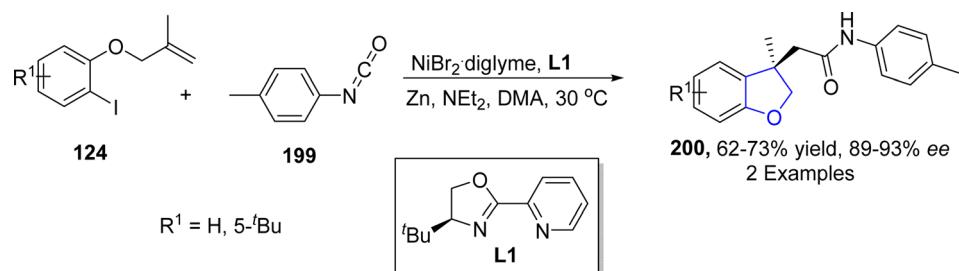
## 2.6. Ru-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives

Ruthenium, though being the rarest earth metal, is widely used as a catalyst in organic transformations. The Ru-catalyzed

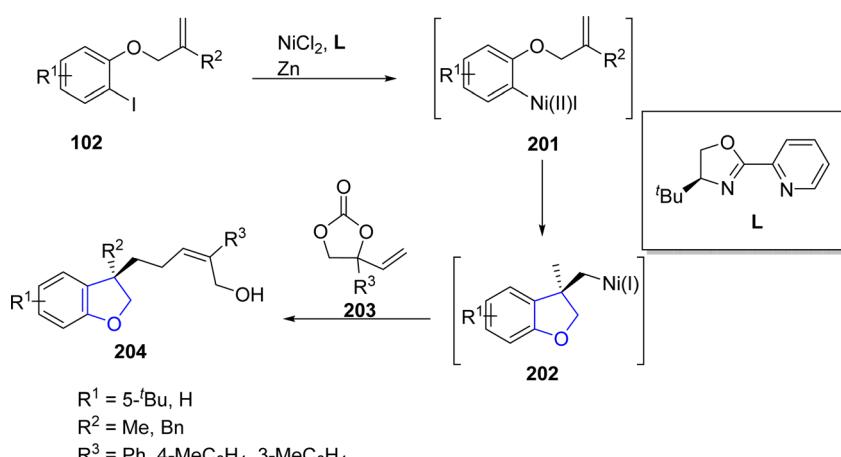
synthesis of dihydrobenzofuran derivatives *via* C–C and C–H bond functionalization has gained tremendous attention in organic synthesis. Directing groups accompanied enantioselective functionalization of C–H bonds promoted by TM catalysts has gained significant utility in several organic transformations. In 2023, Sau<sup>117</sup> *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<sub>6</sub>, 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.*<sup>118</sup> 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).

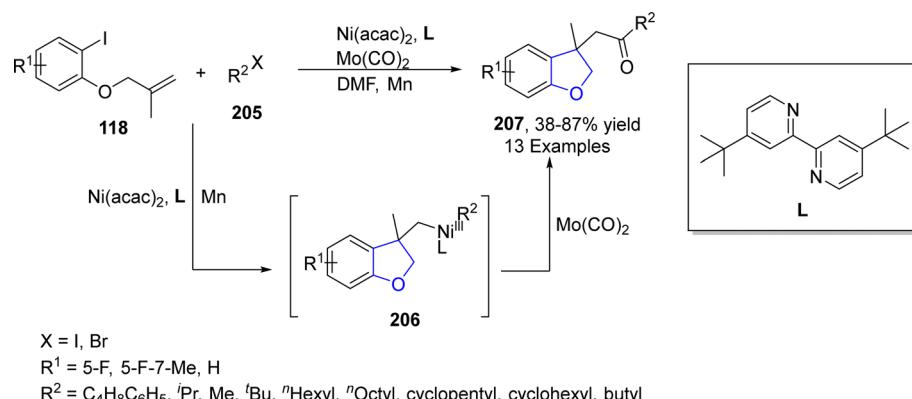
Utilizing the annulation reaction strategy, another ruthenium-catalyzed approach for the facile synthesis of dihydrobenzofurans was demonstrated by Phukon<sup>119</sup> *et al.* in 2023.



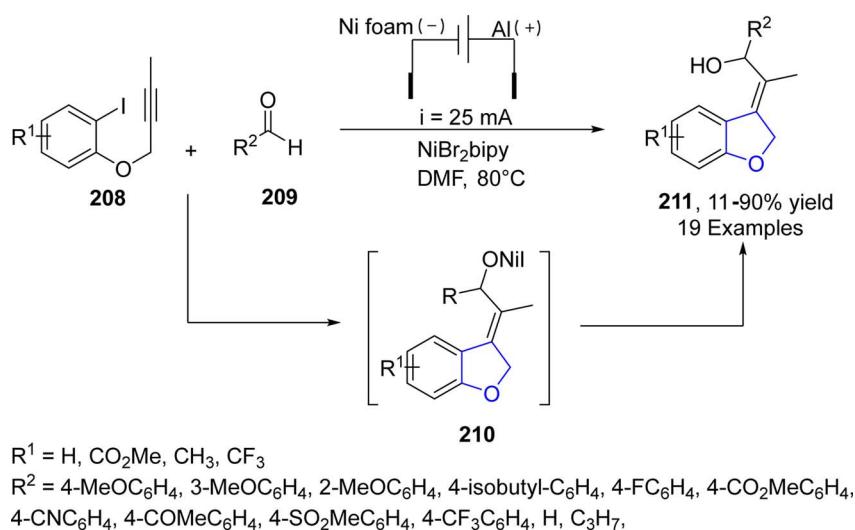
Scheme 43 Synthesis of substituted dihydrobenzofurans 200.



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.

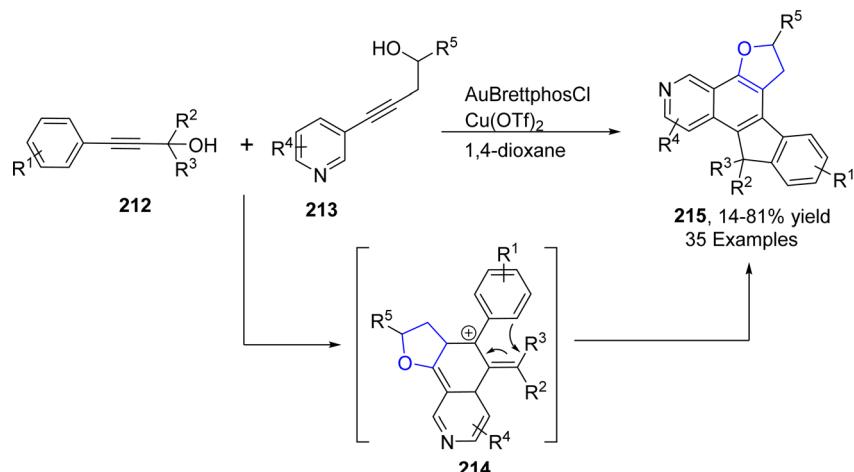
In the developed synthetic methodology, substituted naphthols **234** were made to react with substituted sulfoxonium ylides **233** via the cyclization reaction, which involved the employment of 1,4-dioxane (as a source of  $-\text{CH}_2$ ) and copper acetate to synthesize dihydronaphthofurans **235** in 51–68% yield (Scheme 53).

In 2021, Yuan<sup>120</sup> *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  $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$  as an efficient photocatalyst along with  $\text{CuI}$ /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

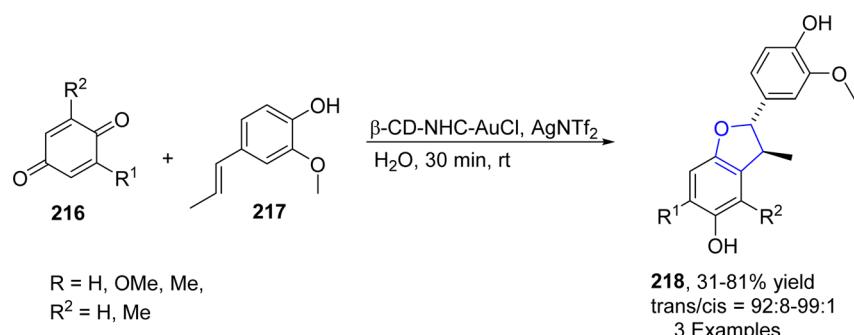
Iridium is the most corrosion resistance metal, which displays variable oxidation states and is utilized as a good catalyst in several organic transformations. Cross-dehydrogenative coupling (CDC) is an efficient approach to afford various organic frameworks by involving the formation of C–C bond *via* two unequal C–H bonds. This synthetic transformation is highly ecofriendly and requires a short duration.<sup>121</sup> 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<sup>122</sup> *et al.* in 2022 presented the enantioselective synthesis of dihydrobenzofurans **242** exploiting intramolecular CDC  $\text{C}(\text{sp}^2)\text{H}/\text{C}(\text{sp}^3)\text{H}$ . 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



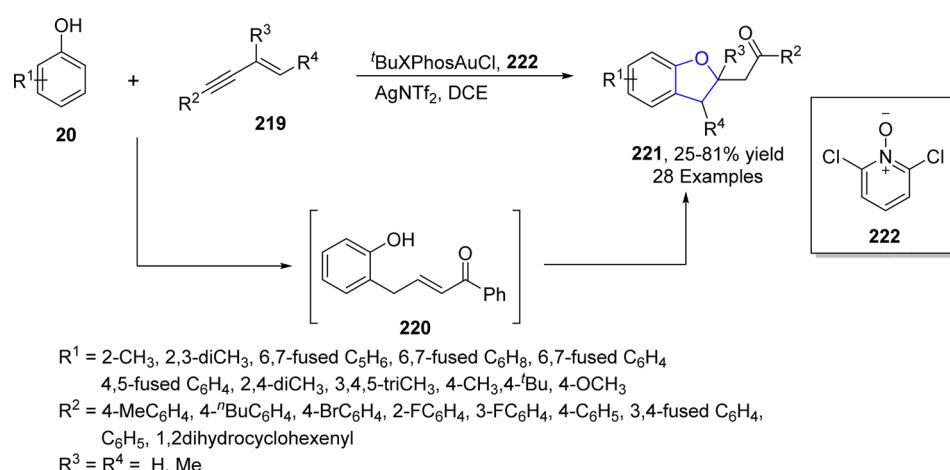


$\text{R}^1 = 10\text{-OMe, 10-F, 11\text{-OMe, 12\text{-OMe, 10\text{-OMe, 10\text{-Me, 12\text{-Me, 10\text{-Et, H, 10,12\text{-diMe, CF}_3, 10\text{-Ph, 10\text{-COOMe, 10\text{-NO}_2, 10-F, 10-Cl, 10-Br, thiophenyl}}}}$   
 $\text{R}^2 = \text{Ph, 4-MeC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 2\text{-ClC}_6\text{H}_4, 4\text{-OMeC}_6\text{H}_4,$   
 $\text{R}^3 = \text{Ph, 4-MeC}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-Ph-C}_6\text{H}_4,$   
 $\text{R}^4 = 6\text{-Me, 6-Cl, 6-F, H}$   
 $\text{R}^5 = \text{Me, diMe, H,}$

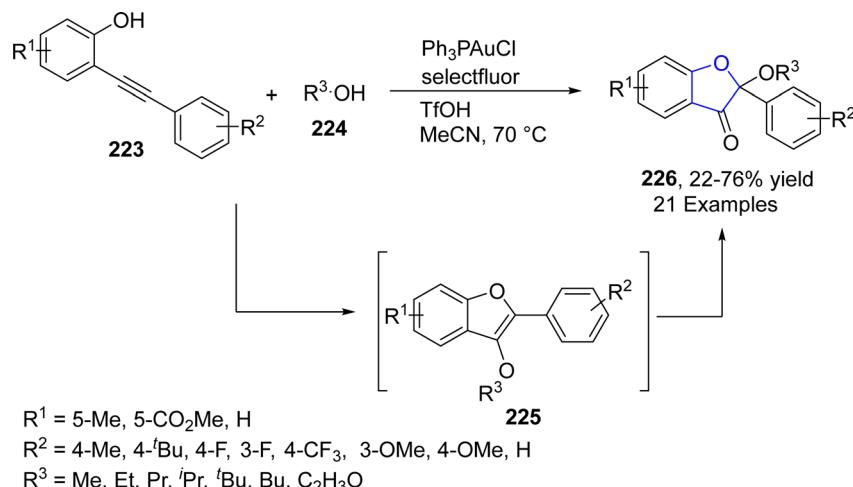
Scheme 47 Synthesis of polycyclic dihydrobenzofuran derivatives 215.



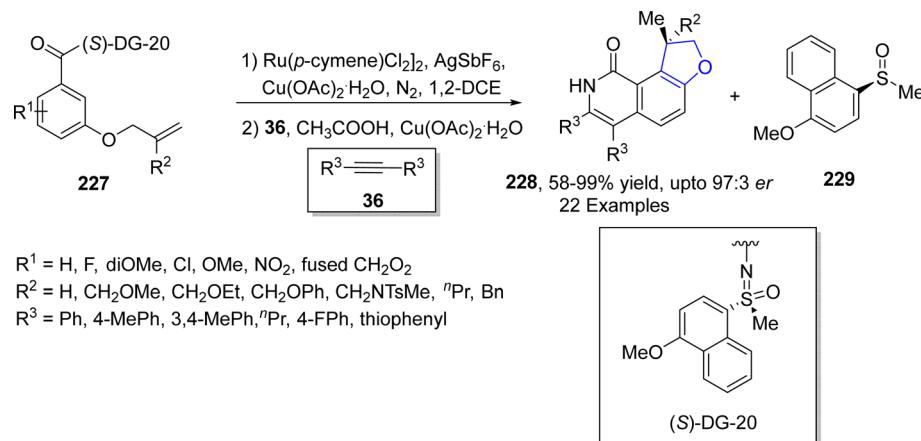
Scheme 48 Synthesis of 2,3-disubstituted dihydrobenzofurans 218.



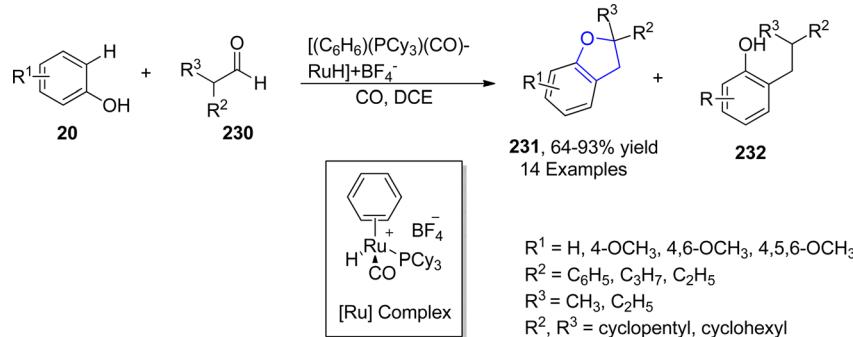
Scheme 49 Synthesis of 2,3-dihydrobenzofuran derivatives 221.



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



Scheme 51 Synthesis of dihydrobenzofuran-fused isoquinolinones 228.

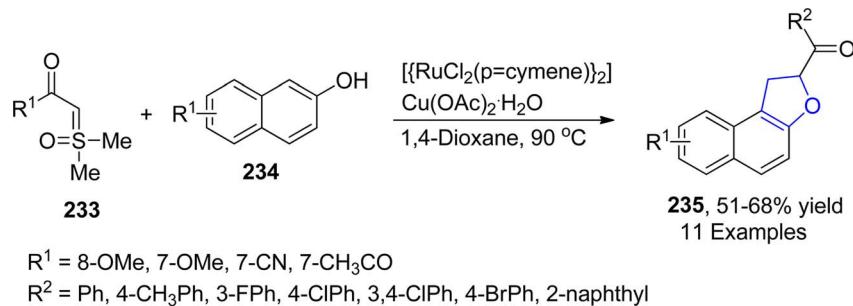


Scheme 52 Synthesis of dihydrobenzofuran heterocycles 231.

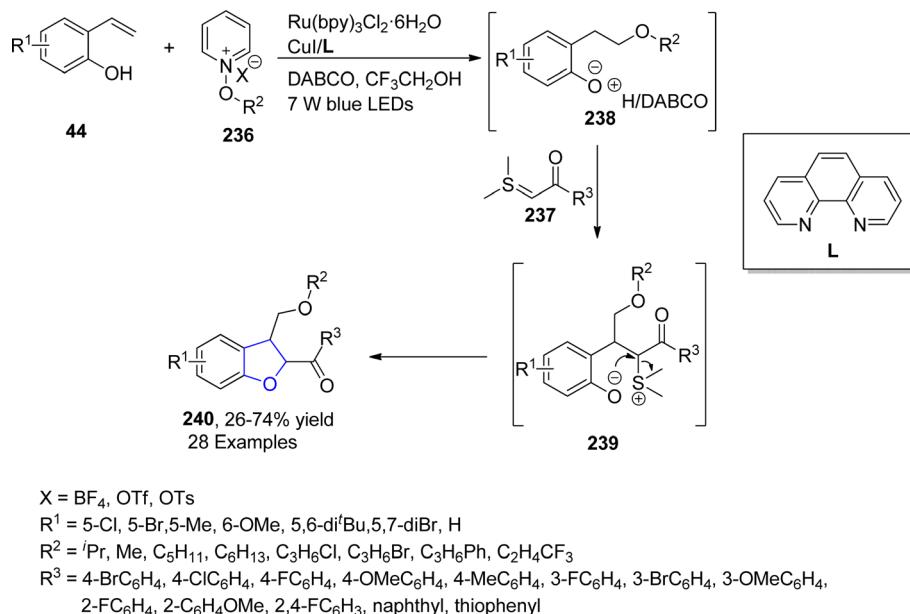
proceed *via* oxidative addition of 241, followed by the removal of hydrogen and ligand exchange, leading towards the synthesis of aryliridium intermediate 242. The intermediate 242 then underwent cyclization and reductive elimination to give dihydrobenzofurans 243 in high enantiomeric excess (up to 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.<sup>123</sup> Utilizing the intramolecular hydroarylation strategy, in 2021, Sakamoto and Nishimura<sup>124</sup> described the Ir-catalyzed, enantioselective synthesis of 2,3-





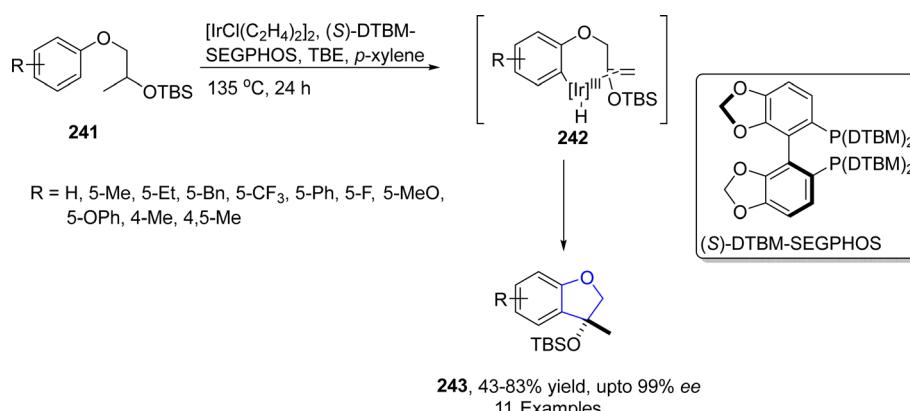
Scheme 53 Synthesis of dihydronaphthofurans 235.



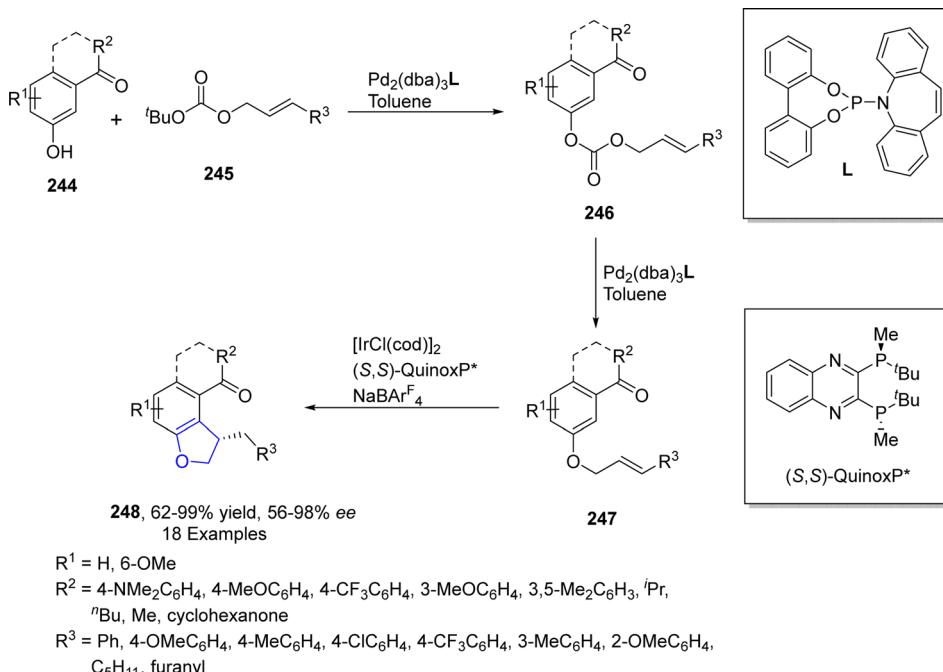
Scheme 54 Synthesis of dihydrobenzofuran derivatives 240.

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*–

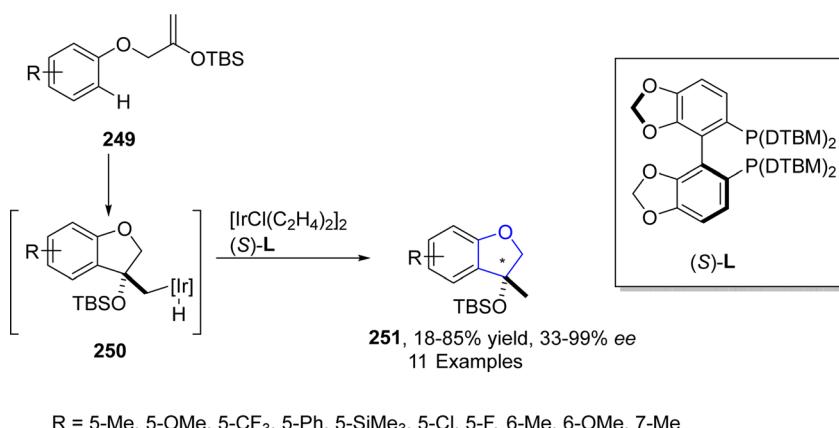
cinnamylxyloxyphenyl ketones **247** from allyl carbonate **246**, followed by the Ir-catalyzed protocol to afford 2,3-dihydrobenzofuran compounds **248**. A bisphosphine ligand, *i.e.*, (*S,S*)-QuinoxP\*, was used to attain higher enantioselectivities (>98% ee) (Scheme 56).



Scheme 55 Synthesis of dihydrobenzofuran derivatives 243.



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



Scheme 57 Synthesis of 2,3-dihydrobenzofuran 251.

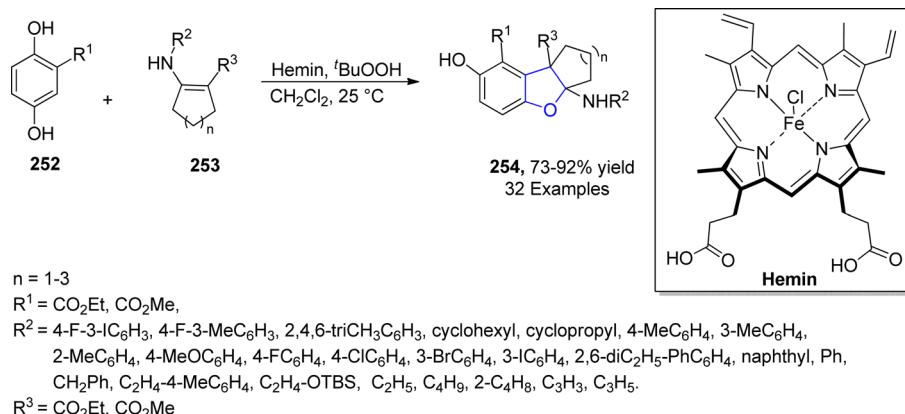
In 2021, Ohmura<sup>125</sup> *et al.* reported the synthesis of enantioselective 2,3-dihydrobenzofuran scaffolds 251 *via* iridium-catalyzed intramolecular hydroarylation. In their novel methodology, *tert*-butyldimethylsilyloxy-substituted aryl ethers 249 acted as starting materials that were transformed 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.<sup>126</sup> Bashir<sup>127</sup> *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<sub>2</sub>Cl<sub>2</sub> (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<sub>50</sub> value = 27.73  $\mu\text{M}$ .

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



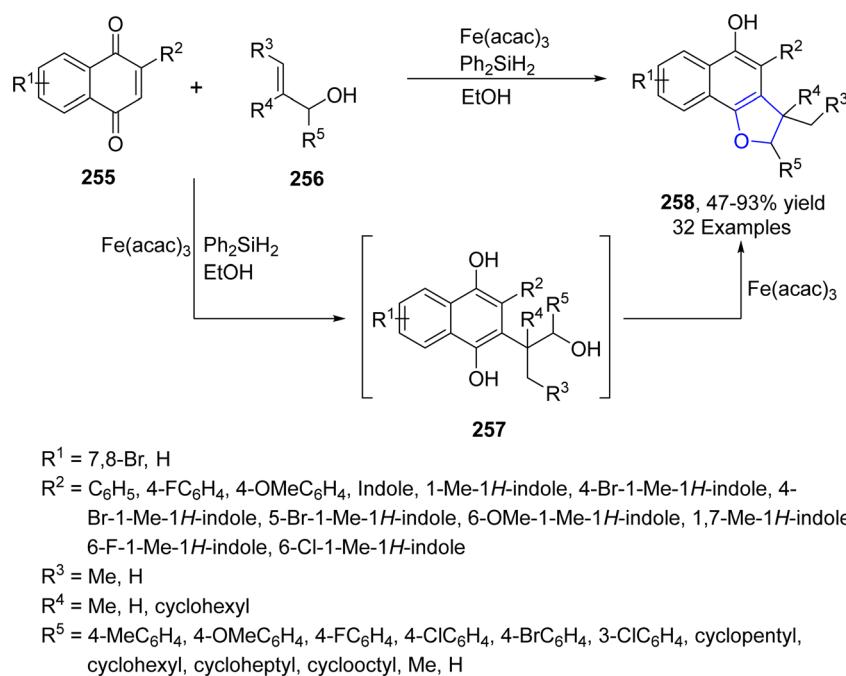
Scheme 58 Synthesis of 2,3-dihydrobenzofuran 254.

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

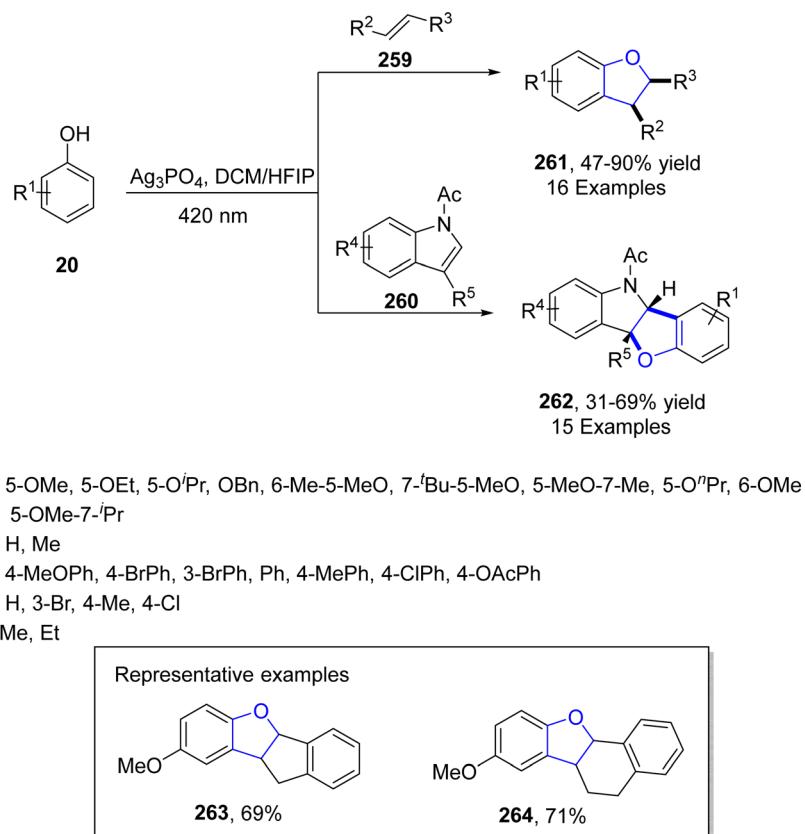
Ag-catalyzed [3 + 2] annulation reactions are the most convenient synthetic strategies for the synthesis of five-

membered heterocyclic ring compounds.<sup>94</sup> In this context, in 2023, Guo<sup>129</sup> *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



Scheme 59 Synthesis of naphthodihydrofurans 258.





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

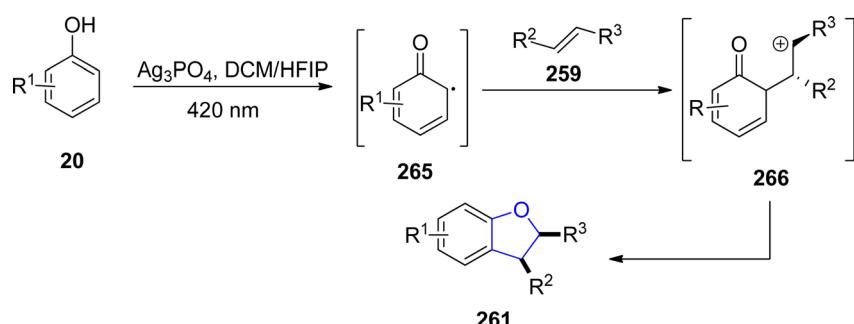
eliminates a proton to furnish the desired 2,3-dihydrobenzofuran derivatives **261** and **262** (Scheme 60). The proposed mechanism of the reaction was supposed to be initiated with the formation of radical species **265**, which cross coupled with the radical cation of **259** to form an intermediate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

In 2021, Dias and coworkers<sup>130</sup> 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

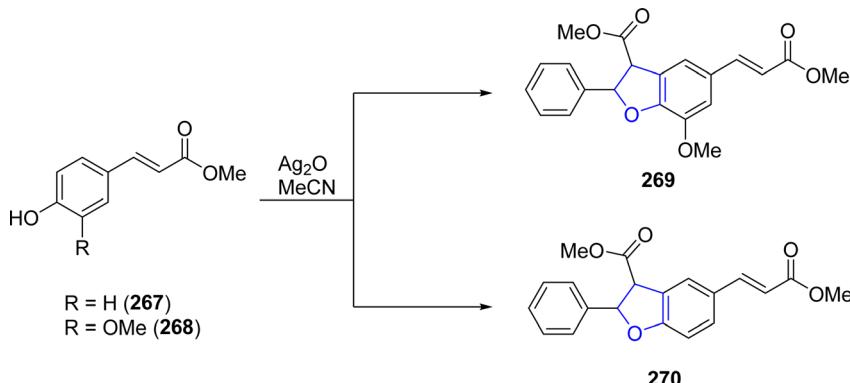
the presence of  $\text{Ag}_2\text{O}$  (used as catalyst) and azobisisobutyronitrile (as radical inhibitor) in acetonitrile. These conditions furnished significant stability between conversion and selectivity (with 45% conversion and more than 71% selectivity) of dihydrobenzofurans **269** and **270** (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.<sup>131</sup> Regarding to this, Okamoto<sup>132</sup> *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.  $\text{Bu}_4\text{NPF}_6$  (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<sup>133</sup> 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  $^7\text{Bu}_4\text{NBF}_4$  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

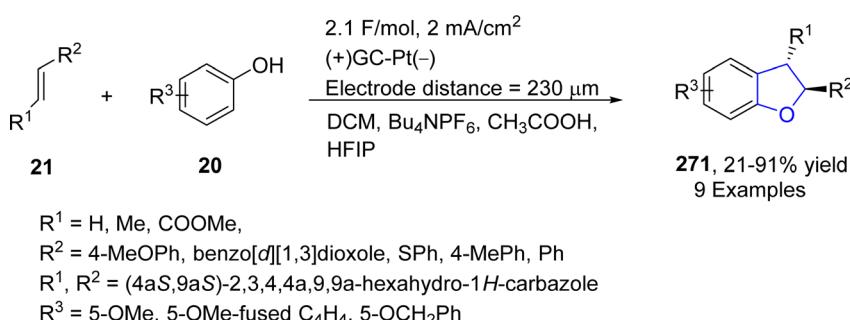
involved the anodic oxidation of substituted aminophenols 272 *via* single electron transfer, followed by an addition reaction with alkenes 273 to form intermediate 274. The resulting intermediate was then supposed to form the carbocation, which ultimately afforded dihydrobenzofurans 275, followed by intramolecular cyclization (Scheme 64).

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

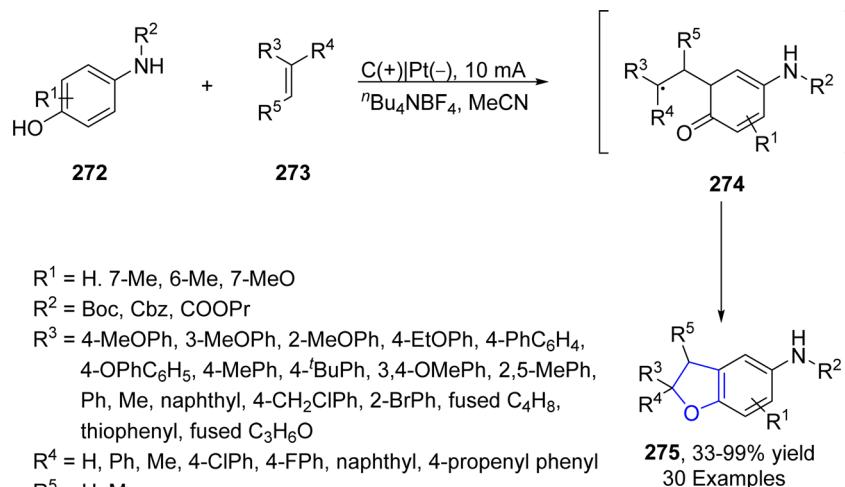
Vanadium (V), being a transition metal, has the capability to change its oxidation state and is used as an efficient catalyst for many reaction systems. Utilizing the V-catalyzed synthetic protocol, Wang<sup>134</sup> *et al.* in 2023, treated the substituted aryl acetates 277 and dihydroxy substituted 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,  $n\text{-Bu}_4\text{NHSO}_4$  and  $\text{B}(\text{OMe})_3$  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

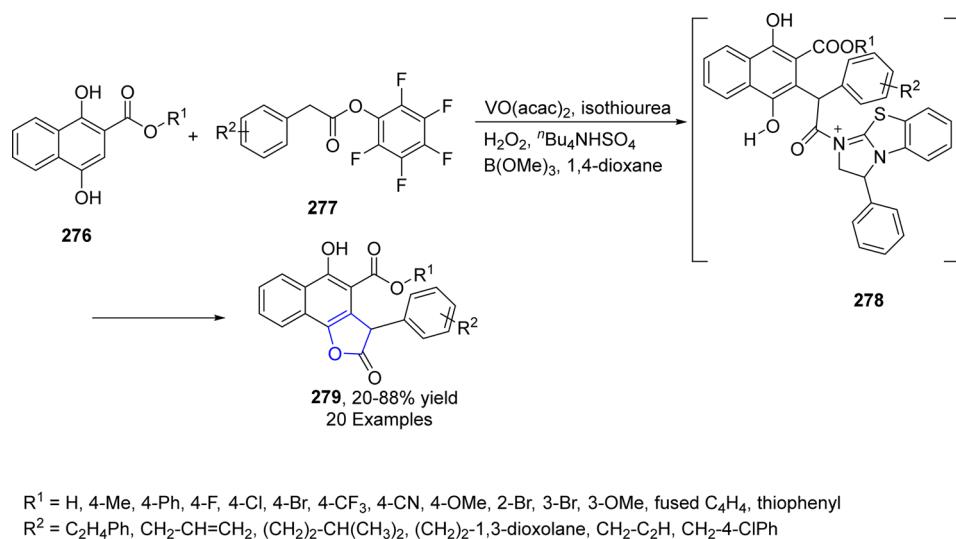
Owing to their inexpensive and reusable characteristics, tungsten (W) catalysts are abundantly used in organic



Scheme 63 Synthesis of dihydrobenzofuran 271.



Scheme 64 Synthesis of dihydrobenzofurans 275.



Scheme 65 Synthesis of polycyclic dihydrobenzofuran 279.

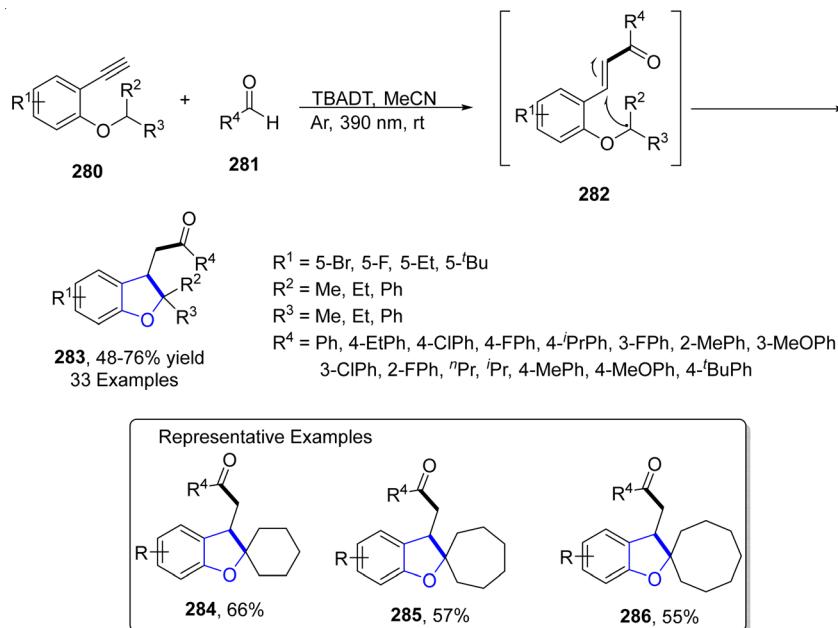
synthesis. Another visible-light promoted synthetic route to achieve dihydrobenzofurans was given in 2023 by Gowda<sup>135</sup> *et al.* For this purpose, diversely substituted aromatic aldehydes **281** were made to react with alkynyl aryl ethers **280** exploiting TBADT (tetrabutylammonium decatungstate), 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<sup>136</sup> *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-propynol-phenols **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 ( $Co(OAc)_2 \cdot 4H_2O$ ), 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.

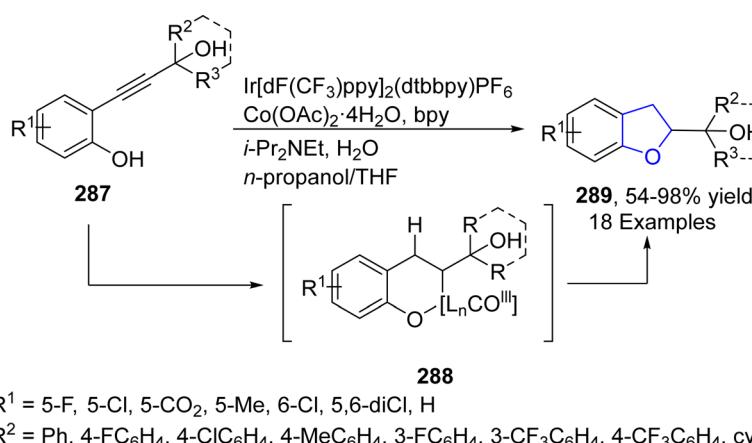
played a vital role for the intramolecular cyclization with (*Z*)-alkene, which was transformed from alkyne group of 287. As per the suggested mechanism, activated Co species underwent hydrometallation with alkyne part of 287, proceeded by protonation and oxidative addition (with phenolic hydroxyl group). 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

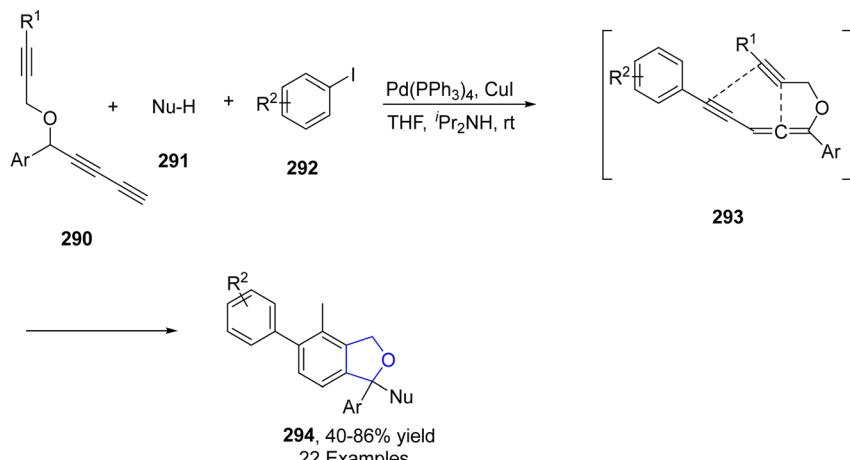
**2.14.1. Pd and Cu-catalyzed synthesis of 2,3-dihydrobenzofuran derivatives.** Phthalans are structurally dihydrobenzofurans constituting organic scaffolds, which are of significant contribution in the pharmaceutical industry. In 2022,

Huang<sup>137</sup> *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



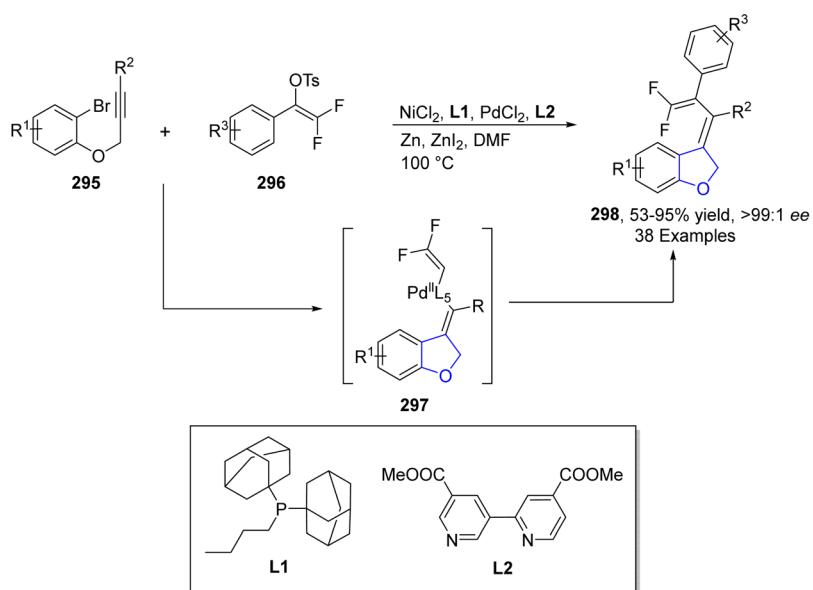
Scheme 67 Synthesis of dihydrobenzofuran derivatives 289.



Scheme 68 Synthesis of substituted phthalans 294.

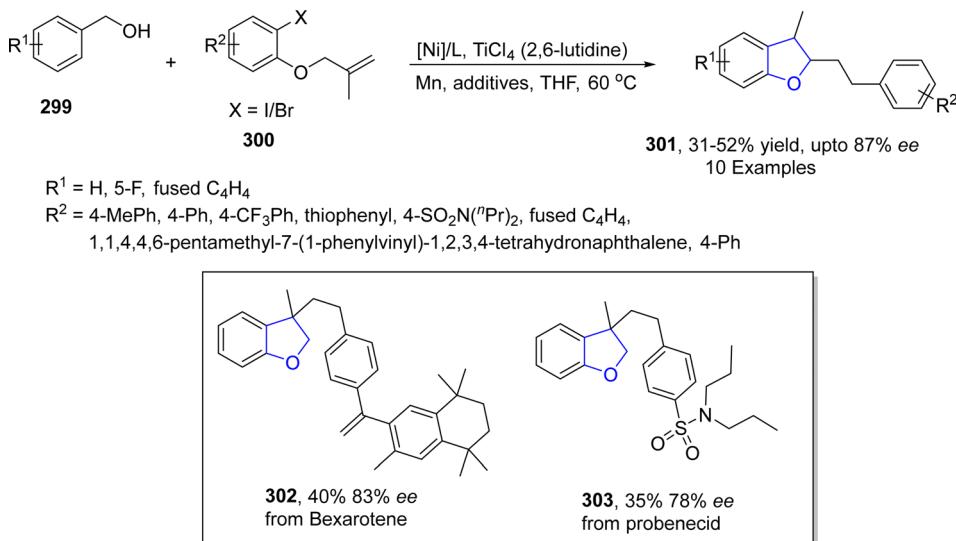
dynamic strategies for the advancement of chemical reactions in organic synthesis. Lian<sup>138</sup> *et al.* in 2022 devised a dual catalytic protocol to synthesize 2,3-dihydrobenzofurans 298 containing *gem*-difluorovinyl framework. In their synthetic approach, the coupling of *gem*-difluorovinyl 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 trans-metallation step to generate *gem*-difluorovinyl zinc intermediate, which interacted with Pd-mediated alkynyl



Scheme 69 Synthesis of 2,3-dihydrobenzofurans 298.





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.<sup>139</sup> Similarly, various catalysts comprising of titanium (Ti) play a crucial role in the development of dihydrobenzofuran core structure.<sup>140</sup> In 2023, Zhao<sup>141</sup> *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  $\text{Ni}(\text{COD})_2$  and titanium chloride ( $\text{TiCl}_4$ ) 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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