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Recent Advances in Phthalan and Coumaran Chemistry

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Oxygen-containing heterocycles are common in biologically active compounds. In particular, phthalan and coumaran cores are found in pharmaceuticals, organic electronics, and other useful medical and technological applications. Recent research has expanded the methods available for their synthesis. This Minireview presents recent advances in the chemistry of phthalans and coumarans, with the goal of overcoming synthetic challenges and facilitating the applications of phthalans and coumarans.

1. Introduction

Oxygen-containing heterocycles have wide-ranging pharmaceutical, industrial, and medical applications. In particular, the 1,3-dihydroisobenzofuran (phthalan) structural motif is present in a variety of antioxidant[1] and antidepressant[2,3] compounds. Phthalan derivatives such as citalopram[2] and escitalopram[3] are antidepressant drugs of the selective serotonin reuptake inhibitor class. Additionally, the isofuran component may be useful for functionalization and helicity[4] in some molecules. A phthalan core can also be incorporated into conjugated polymer semiconductors[5,6] for optoelectronic and electrochemical devices such as organic solar cells, light-emitting diodes, field-effect transistors, and chemo- and biosensors.

Coumarans (2,3-dihydrobenzofurans) have antitubercular[7–9] and anti-HIV[10] activity. The dihydrobenzofuran skeleton has wide-ranging medical uses. For example, megapodiol is an anti-leukemic agent,[11] Conocarpan is an anticancer agent,[12] and the furaquinocines are antibiotics.[13] Other derived compounds exhibit cytotoxic and antiprotozoal activities.[14] Phthalan and coumaran cores have also been used as building blocks.[15,16]

Recent advances in the chemistry of phthalans and coumarans are presented in this Minireview, with a focus on articles from 2012 to the present. To our knowledge, only two reviews on phthalans have been published.[17,18] This Minireview includes cyclization reactions as well as transformations of furans and indolines. To the best of our knowledge, the last two comprehensive reviews concerning coumaran synthesis were published in 2009 and 2011.[19,20] The most recent review[21] focuses on palladium-catalyzed cyclization to yield various heterocyclic systems, including coumarans, but does not discuss alternative preparatory routes.

2. Synthetic Routes to Phthalans

As aforementioned, 1,3-dihydroisobenzofurans (phthalans) include many natural products that exhibit fascinating pharmacological activities, including antidepressant, antioxidant, antifungal, antibacterial, antitumor, and anti-inflammatory properties; treatment of cardiovascular disease; and so on. They are also industrially important and are major building blocks in organic synthesis. Figure 1 represents some selected pharmacologically active phthalans.

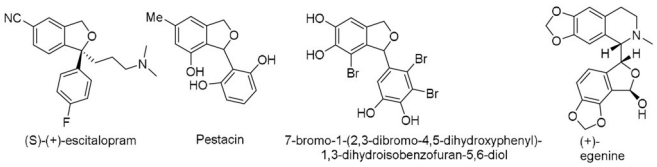

Figure 1. Phthalan-based pharmacologically active compounds.

Owing to such versatile applications, the development of efficient and economic methods for phthalan synthesis has attracted considerable research effort. Many transition-metal catalysts and metal-free strategies are available for the construction of substituted phthalans, and several procedures for the synthesis of the phthalan core are available, including cycloaddition reactions, Garratt–Braverman cyclization, transformations, and reduction reactions.

2.1. Transition-Metal-Catalyzed [2+2+2] Cycloaddition

Transition-metal-catalyzed [2+2+2] cyclotrimerization is a powerful strategy for synthesizing substituted benzenes, in-

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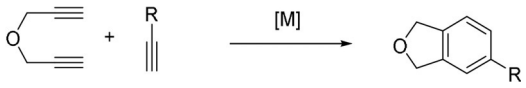
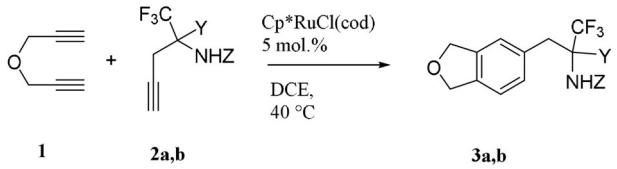
cluding phthalans. For example, the [2+2+2] cyclotrimerization of alkynes has successfully been investigated with various transition metals (Scheme 1). This cyclotrimerization can be either intra- or intermolecular. In the following paragraphs, we present selected Co/Rh/Ru/Ir-catalyzed [2+2+2] cyclotrimerizations of 1,6-diynes and alkynes for phthalan synthesis.



Scheme 1. Transition-metal-catalyzed [2+2+2]-cycloaddition reaction of unsaturated substrates for phthalan formation.

Zotova et al. report that ruthenium-catalyzed cyclotrimerization of aminopropargyltrifluoromethyl carboxylates **2a** and **2b** and phosphonates with functional 1,6-diyne **1** gives the corresponding CF_3-containing phenylalanine derivatives and phosphorus analogues **3a** and **3b**.[22] The formation of phthalans **3a** and **3b** proceeds in 1,2-dichloroethane (DCE) at 40 °C in good yields (Scheme 2) with 70–75% conversion.

This methodology has been applied for the reactions between ethynyl *N*-methyliminodiacetic acid (MIDA) boronate **4**



1 **2a,b** **3a,b**

2,3 a: Y=CO_2Me, Z=Boc
2,3 b: Y=P(O)$(OEt)_2$, Z=Cbz

Scheme 2. Ruthenium-catalyzed cyclotrimerization of aminopropargyltrifluoromethyl carboxylates and phosphonates with 1,6-diynes. cod = cyclooctа-1,5-diene, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

with 1,6-diynes **1**[23] (Scheme 3). Along with Cp*Ru(cod), $[Rh(cod)_2]BF_4$/BINAP can also be used as the catalyst. In this case, the yield increases from 53 to 64%. The authors report the use of an excess amount of compound of **4** and 2 equivalents of **5a** and **5b**, respectively.

In the context of complex catalytic systems, Du et al.[24] describe the synthesis of a catalyst based on a metal–organic framework (MOF). This is an increasingly important class of porous crystalline materials with exceptional surface areas and uniformly dispersed metal ions. A MOF catalyst based on

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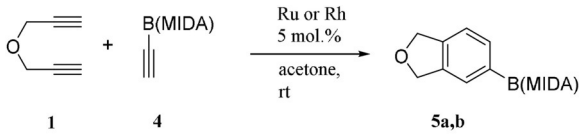
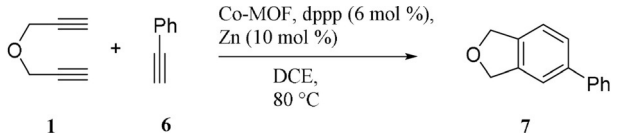


5 a: Ru=Cp*RuCl(cod)
5 b: Rh=$[Rh(cod)_2]BF_4$/BINAP

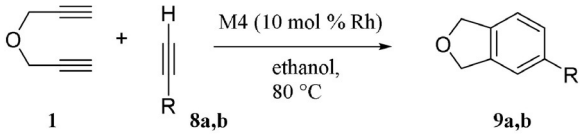
Scheme 3. Cyclotrimerization of MIDA boronate **4** with 1,6-diyne **1**. Cp* = η^5-pentamethylcyclopentadienyl, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

cobalt is effective for the [2+2+2] cycloaddition of 1,6-diyne **1** and various substituted alkynes **6**[24] (Scheme 4). The optimal reaction conditions are Co-MOF-10 (10 mg), 1,3-bis(diphenylphosphino)propane (dppp, 6 mol%), and Zn powder (10 mol%) in DCE (2.0 mL) at 80 °C for 24 h. 1,6-Diyne **1** reacts with phenylacetylene (**6**) to form phthalan **7** in 84% yield.



Scheme 4. Application of a Co-MOF catalyst in phthalan synthesis.

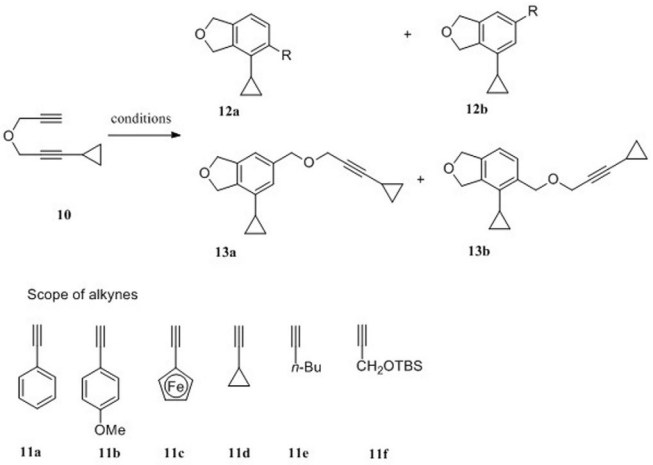
Roglans et al. presented another complex catalyst in 2014.[25] They detail the use of a rhodium N-heterocyclic carbene (Rh-NHC) hybrid silica recyclable catalyst, that is, M4, for the [2+2+2]-cycloaddition reactions of alkynes **8a** and **8b** (Scheme 5). The yield of phthalans **9a** and **9b** in this cycloaddition of 1,6-diyne **1** with substituted acetylenes **8a** and **8b** can be 100%. The protocol is to separate the catalytic system from the reaction mixture by simple filtration to afford an analytically pure product. The catalyst can be reused up to six times without any decrease in the yield of the cycloadduct.



9a: R=CH_2OH (reaction time 2h) Yield 100%
9a*: R=CH_2OH (reaction time 4.5h) Yield 85%
9b: R=Ph (reaction time 1h) Yield 50%
* - second round of catalyst use

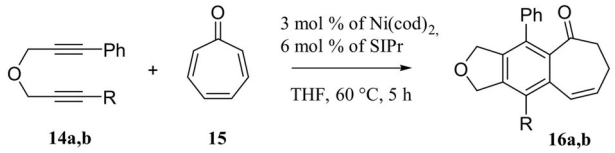
Scheme 5. Phthalan synthesis with the use of a Rh-NHC hybrid silica recyclable catalyst.

In 2016, Matousova et al.[26] investigated the cyclotrimerization of 1-cyclopropyl-1,6-diynes **10** with terminal alkynes **11a–f** catalyzed by Wilkinson's catalyst $[RhCl(PPh_3)_3]$, $Rh(cod)_2BF_4$/BINAP, $CpCo(CO)_2$ (Cp = η^5-cyclopentadienyl), and $NiBr_2(PPh_3)_2$/Zn to prepare phthalans **12a** and **12b**. They report that isomers **13a** and **13b** are formed in 4–26% yield (Scheme 6).



Scheme 6. Cyclotrimerization of 1-cyclopropyl-1,6-diyne **10** with various terminal alkynes **11**. For unsymmetrical acetylenes, cycloaddition is not regioselective. In addition, except for cyclotrimerization, alkylation occurs. Products **13a** and **13b** are obtained in up to 63% yield. TBS = *tert*-butyldimethylsilyl.

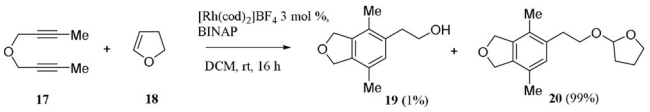
Along with acetylenes in [2+2+2]-cycloaddition reactions, other 2π substrates can be used. In 2014, Kumar et al. elaborated a protocol involving the Ni(NHC)-catalyzed cycloaddition of diynes **14a** and **14b** and tropone (**15**) to form substituted benzenes, including phthalans **16a** and **16b** in 81–86% yield[27] (Scheme 7). The reaction conditions include the use of a diyne (1 equiv), tropone (1.1 equiv), $Ni(cod)_2$ (3 mol%), and 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene (SIPr, 6 mol%) in THF at 60 °C for 5 h. The regioselectivity reaches 95%.



14,16a: R=Me
14,16b: R=Et

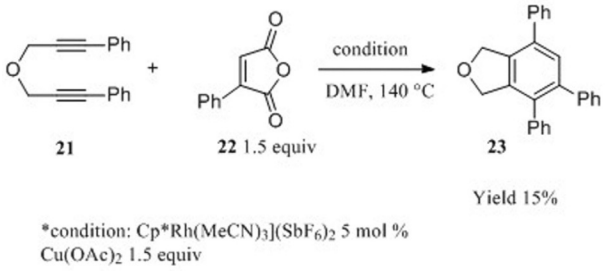
Scheme 7. Ni-catalyzed cycloaddition of diynes and tropone.

In 2016, Tanaka's group investigated the same approach further. They disclose the rhodium-catalyzed [2+2+2] cycloaddition–aromatization of 1,6-diyne **17** with 2,3-dihydrofuran (**18**)[28] (Scheme 8). This reaction affords substituted phthalan **20** in 53% yield with 99% regioselectivity. The cycloaddition–aromatization occurs with subsequent acetalization at room temperature to give corresponding protected 2-arylethanol **20**, along with a trace amount of unprotected 2-arylethanol **19**.



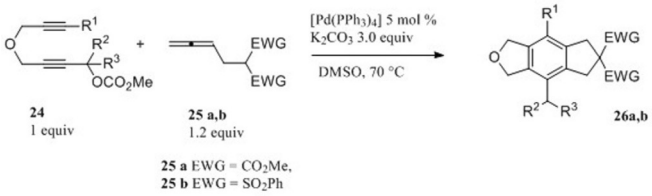
Scheme 8. Rhodium-catalyzed [2+2+2] cycloaddition–aromatization of 1,6-diynes with 2,3-dihydrofurans.

This methodology has been applied for the rhodium(III)-catalyzed [2+2+2] cyclotrimerization of 1,6-diyne **21** with maleic anhydrides **22** as alkyne equivalents[29] to give 1,3-dihydroisobenzofurans **23** (Scheme 9).



Scheme 9. Cyclotrimerization of 1,6-diyne with maleic anhydride.

Aside from alkynes and alkenes, substrates such as allenes can take part in [2+2+2]-cycloaddition reactions for the synthesis of substituted benzenes. Huang et al.[30,31] outline the development of an efficient method for the synthesis of fused tricycles **26a** and **26b** on the basis of palladium-catalyzed tandem reactions of 2,7-alkadiynylic carbonates **24** with allenes **25** bearing a carbon nucleophile (Scheme 10).

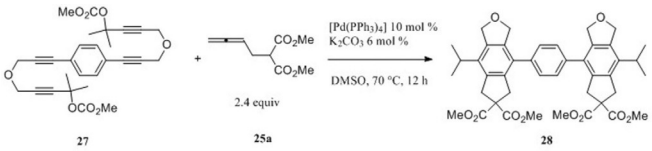


Scheme 10. Palladium-catalyzed tandem reactions of 2,7-alkadiynylic carbonates with allenes bearing a carbon nucleophile.

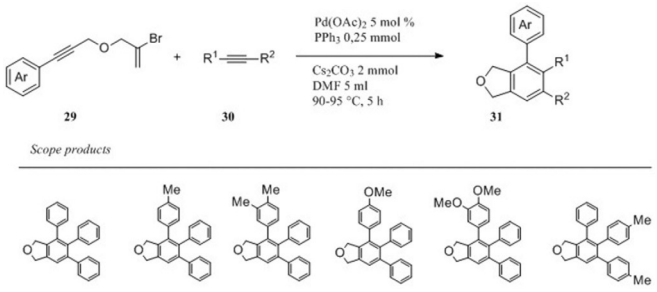
The same methodology has been used to construct six-ring compound **28** starting from alkynes **27** (Scheme 11).

In 2015, Ray et al. developed an efficient heteroannulation protocol for the construction of 4,5,6-trisubstituted-1,3-dihydroibenzofurans **31** through the palladium-catalyzed domino carbopalladation of bromoenynes **29** and internal alkynes **30**[32] (Scheme 12).

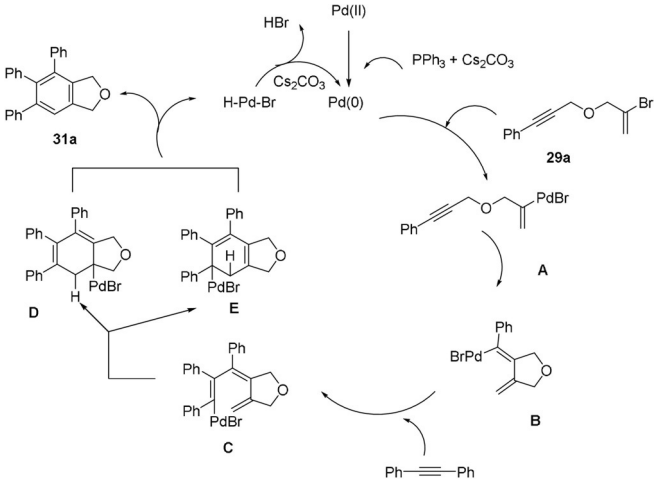
A plausible mechanism involves the formation of Pd^0 from Pd^{II} by reducing PPh_3, which enters the catalytic cycle by oxidative addition to the C(sp^2)–Br bond of bromoenyne **29a**; this leads to the formation of alkenylpalladium intermediate **A** (Scheme 13). Intermediate **A** then undergoes an intramolecular transformation to form alkenylpalladium intermediate **B**. Carbopalladation of diphenylacetylene **30** to **B** furnishes intermediate **C**, which is then converted into desired product **31a** either via **D** (6-*endo-trig* carbopalladation) or **E** (6π-electrocyclization), followed by a β-dehydropalladation sequence.



Scheme 11. Construction of a six-ring compound by a one-step protocol.

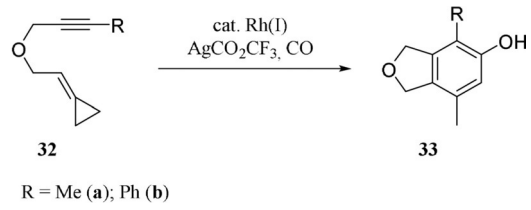


Scheme 12. Synthesis of 4,5,6-trisusbstituted-1,3-dihydroisobenzofurans.



Scheme 13. Plausible mechanism for the formation of 4,5,6-triphenyl-1,3-dihydroisobenzofurans.

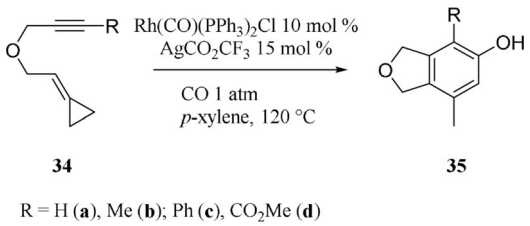
In 2014,[33] the Chung group developed a novel Rh-catalyzed carbonylative [3+2+1] cycloaddition of alkyne-tethered alkylidenecyclopropanes **32** for the facile synthesis of bicyclic phenols **33** in high yields under mild reaction conditions (Scheme 14).



Scheme 14. Rh^I-catalyzed [3+2+1]-cycloaddition reactions.

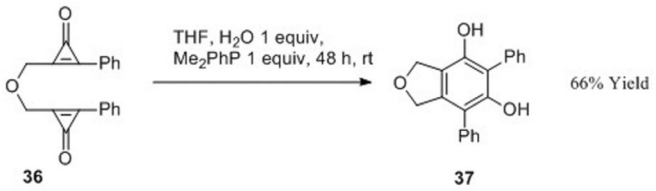
The Negru group describes the use of the same methodology[34] for the carbonylative [3+2+1] cycloaddition of alkylidenecyclopropanes **34** to give bicyclic phenols **35** (Scheme 15).

In 2013, Shi's group[35] presented a novel phosphine-promoted intramolecular cyclization of dicyclopropenone **36** with the



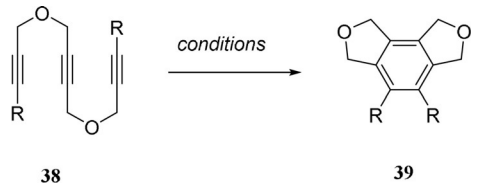
Scheme 15. Rhodium-catalyzed [(3 + 2) + 1] carbocyclization reaction with alkylidenecyclopropanes.

formation of phthalan **37** in 66% yield. Reaction conditions include the use of THF as the solvent, H_2O (1 equiv), and Me_2PhP (1 equiv) as the ligand (Scheme 16).



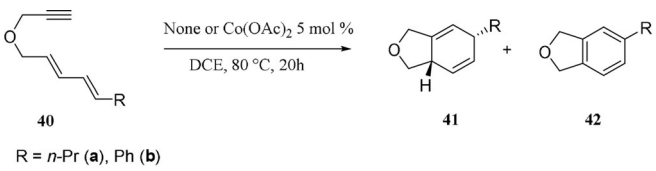
Scheme 16. Phosphine-promoted cyclization of dicyclopropenones.

Chiral cobalt(I)-based complexes and their evaluation in asymmetric [2+2+2]-cycloaddition reactions of alkynes have been presented.[36–38] These complexes are widely used for asymmetric catalysis, including for the synthesis of phthalans **39** from trialkynes **38** (Scheme 17).



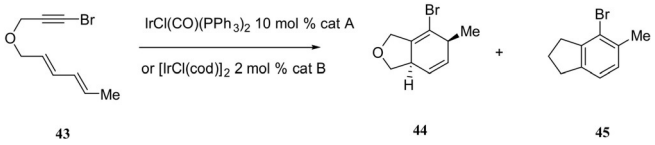
Scheme 17. Intermolecular cycloaddition of triynes **38**.

Along with direct synthesis, phthalans have been observed as side products in some protocols. Biletskyi and co-workers[39] demonstrate that dienynes **40** can undergo intramolecular reactions to form two classes of products, tetrahydroisobenzofurans **41** and phthalans **42**, through a catalytic system including cobalt salts and various ligands (Scheme 18). The researchers note that this is the first example of a cobalt-mediated intramolecular Diels–Alder cycloaddition. This reaction requires $Co(OAc)_2$ as the catalyst, DCE as the solvent, and a temperature of 80 °C. Dienynes possessing a substituent on the alkyne do not react without cobalt, and ZnI_2 as a Lewis acid is required to activate the catalyst.



Scheme 18. Cobalt-mediated intramolecular Diels–Alder cycloadditions of substituted dienynes.

Tigchelaar et al.[40] disclose an investigation into the intramolecular [4+2] cycloadditions of diene-tethered alkynyl halides **43** catalyzed by iridium, specifically with the use of $[IrCl(cod)]_2$ or $IrCl(CO)(PPh_3)_2$ as the catalyst and PPh_3 or BINAP as the ligand (Scheme 19, Table 1). These results are the first examples of the cycloadditions of alkynyl halides by using an iridium catalyst. Tigchelaar et al. determine that aromatic product **45** is formed along with nonaromatic product **44** in 12–26% yield.



Scheme 19. Iridium catalysis for the [4+2] cycloaddition of alkynyl bromides.

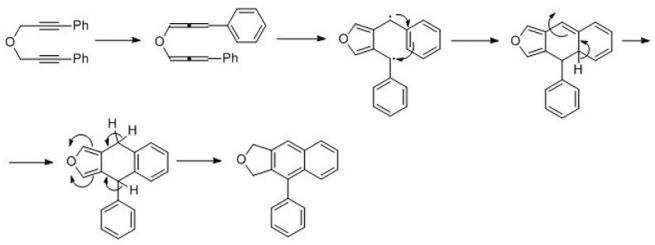
Table 1. Iridium catalysts for the [4+2] cycloaddition of alkynyl bromides.

Entry	Catalyst	Additive/ligand	Solvent	*T* [°C]	Time [h]	Yield [%]	
						44	**45**
1	$IrCl(CO)(PPh_3)_2$	none	toluene	90	18	35	12
2	$IrCl(CO)(PPh_3)_2$	none	toluene	90	3	60	26
3	$[IrCl(cod)]_2$	PPh_3	toluene	90	3	23	17
4	$[IrCl(cod)]_2$	BINAP	toluene	90	3	28	18

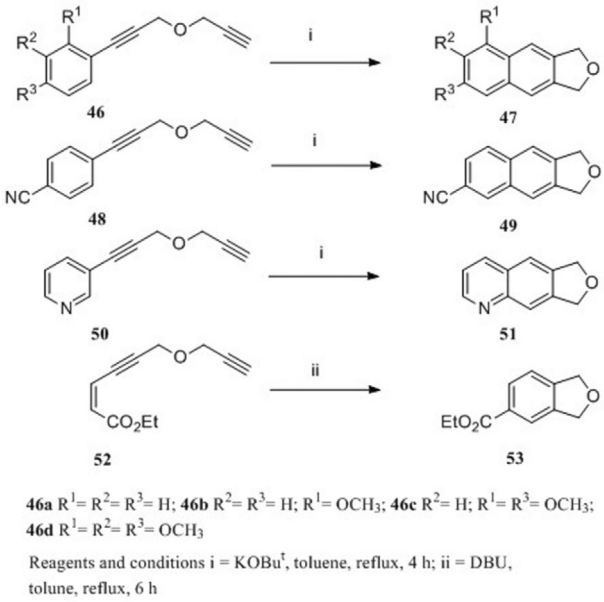
2.2. Garratt–Braverman and Related Reactions

A synthetic approach toward benzo-fused phthalans is the Garratt–Braverman (GB) cyclization, which includes a base-promoted cyclization of bis(3-arylpropargyl) ethers such as **46**, **48**, **50**, and **52** (Scheme 20).

The Basak group[41–43] has made important contributions in this context. In particular, they have developed protocols for preparing aromatic phthalans such as **47** and **49**, heteroaromatic phthalans such as **51**, and aliphatic-connected phthalans such as **53** (Scheme 21). These reactions require use of such bases as KO*t*Bu and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene as the solvent, and elevated temperatures.

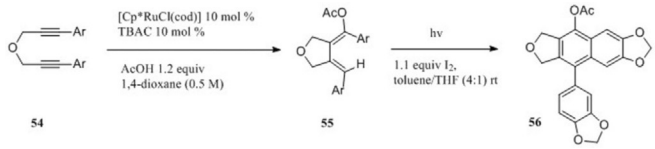


Scheme 20. Mechanism for GB cyclization of aryl-substituted bis-propargyl systems.



Scheme 21. Synthesis of phthalans by GB cyclization.

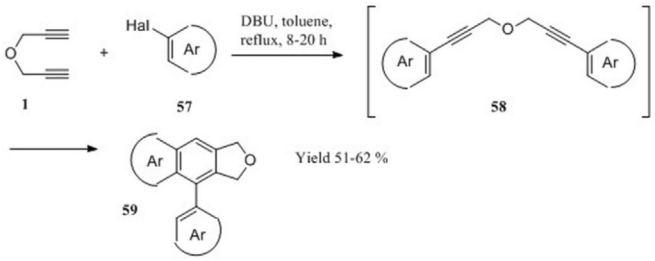
In 2015, Shibuya et al.[44] reported a combined transition-metal-catalyzed and photo-promoted process for preparing hetero-fused phthalan **56** (Scheme 22). In their report, they show that the first hydrocarboxylative cyclization of 1,7-diaryl-1,6-diynes **54** is optimized for the highly stereoselective formation of exocyclic dienyl acetates **55** by using the [Cp*RuCl(cod)] catalyst with nBu$_4$NCl as an additive. Subsequent oxidative photocyclization of the resulting exocyclic dienyl acetates efficiently affords desired 2,3-fused 4-phenylnaphthalen-1-yl acetates **56** if the reaction is performed with I_2 in a mixed solvent of toluene and THF.



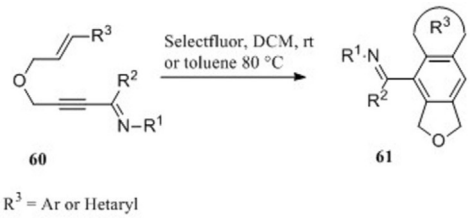
Scheme 22. Ruthenium-catalyzed hydrocarboxylative cyclization of 1,7-diaryl-1,6-diynes and subsequent oxidative photocyclization. TBAC = tetrabutylammonium chloride.

Basak et al. report a tandem Sonogashira coupling and GB cyclization sequence to produce four C–C bonds leading to the synthesis of aryl dihydroisofurans **59**[45] (Scheme 23). Phthalans **59** are synthesized in a one-pot protocol in 51–62% yield from ether **1** and corresponding halogenated aryls **57** via alkynyl ethers **58**.

Zhou et al. delineate Selectfluor-promoted sequential reactions to produce fused polycyclic skeletons **61** via allene intermediates by a metal-free construction[46] (Scheme 24). The reactions are performed by using **60** (0.2 mmol) and Selectfluor (0.22 mmol) in CH_2Cl_2 (2.5 mL) at room temperature or in toluene (2.5 mL) under a N_2 atmosphere at 80 °C.



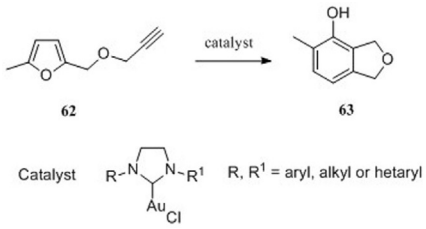
Scheme 23. One-pot synthesis of naphthoisofurans **59**.



Scheme 24. Construction of dihydronaphtho[2,3-c]furans.

2.3. Transformation of Furans into Phthalans

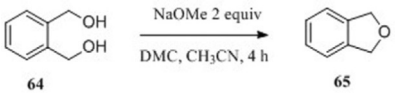
Scheme 25 shows the general transformation of furans **62** into phthalans **63**.[47–57] Typical reaction conditions include the use of a gold-based catalyst and a chlorine-containing solvent, such as $CHCl_3$ or CH_2Cl_2, at room temperature. The structure of the catalyst is a complex compound based on imidazole, in which various aromatic, aliphatic, or heteroaromatic substituents are connected to the nitrogen atoms.



Scheme 25. Catalyzed isomerization of furanynes into phthalans.

2.4. Cyclization of Diols

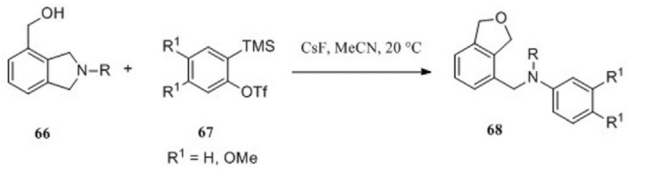
Tonachini et al.[58] report an interesting synthetic protocol for phthalans. The reaction of 1,4-diol **64** with dimethyl carbonate (DMC) in the presence of a base (NaOMe) under mild conditions leads to corresponding phthalan **65** in high yields within a short reaction time (Scheme 26).



Scheme 26. Cyclization of diols.

2.5. Transformation of Indolines

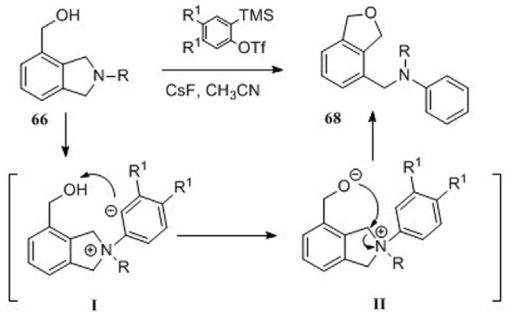
In 2015, Voskressensky et al. presented a method for the intramolecular transformation of 4-hydroxymethyl isoindolines **66**.[59] The authors show that 2-alkyl- and 2-aryl-substituted 4-hydroxymethylisoindolines **66** smoothly undergo intramolecular recyclization through reaction with arynes **67** to give isobenzofurans **68** in good yields (Scheme 27).



R = Et, *i*-Pr, *n*-Pent, $(CH_2)_3OMe$, *c*-C_3H_5, *c*-C_5H_9, Ph, 2-Me-C_6H_4, 4-*i*-Pr-C_6H_4, 4-F-C_6H_4, 4-OMe-C_6H_4, 3-CF_3-C_6H_4, 3-Cl-C_6H_4, Bn, 3,4-$(OMe)_2$-$C_6H_3CH_2$, 2,3-$(Cl)_2$-$C_6H_3CH_2$, $(CH_2)_2$-C_6H_4

Scheme 27. Synthesis of phthalans from indolines. Tf = triflyl.

The reaction starts with Michael addition of the aryne to the tertiary N atom of the starting compound; this is followed by abstraction of H^+ from the hydroxy group in intermediate **A**. Resulting zwitterion **B** undergoes intramolecular recyclization to yield the corresponding phthalan derivative (Scheme 28).

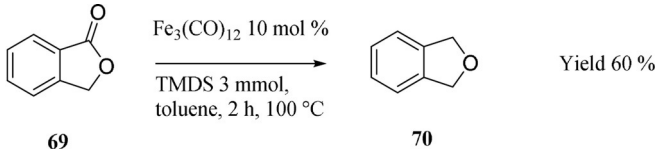


Scheme 28. Proposed mechanism for the intramolecular transformation of isoindolines.

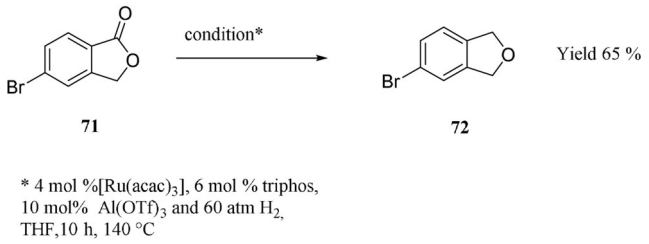
2.6. Reduction of Phthalides to Phthalans

In 2012, the Beller group[60] presented an interesting approach toward phthalans **70** from phthalides **69** through Fe-catalyzed hydrosilylation (Scheme 29).

In 2015, the Beller group also reported the ruthenium(II)-catalyzed formation of phthalan **72** from bromophthalide **71** promoted by a Lewis acid through selective hydrogenation (Scheme 30).[61]



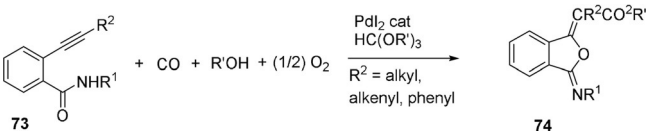
Scheme 29. Iron-catalyzed reduction of esters. TMDS = 1,1,3,3-tetramethyldisiloxane.



Scheme 30. Ruthenium(II)-catalyzed formation of phthalans from phthalides. acac = acetylacetonate, triphos = bis(2-diphenylphosphinoethyl)phenylphosphine.

2.7. Miscellaneous

A rare reaction towards substituted phthalans **74** is presented by Mancuso.[62] 3-[(Alkoxycarbonyl)methylene]isobenzofuran-1(3*H*)-imines are selectively obtained if the oxidative carbonylation of 2-alkynylbenzamides **73**, bearing a terminal or an internal triple bond, is performed in the presence of an alcohol (e.g., such as methanol or ethanol) as the external nucleophile and $HC(OR')_3$ as a dehydrating agent, which is necessary to avoid substrate hydrolysis (Scheme 31). In this case, the pathway leading to the isobenzofuranimine corresponds to 5-*exo-dig* intramolecular nucleophilic attack of the oxygen atom of the benzamide moiety on the triple bond coordinated to the metal center followed by alkoxycarbonylation.



Scheme 31. Synthesis of 3-[(alkoxycarbonyl)methylene]isobenzofuran-1(3*H*)-imines by the PdI_2-catalyzed O-heterocyclization/alkoxycarbonylation of 2-alkynylbenzamides.

3. Synthetic Routes to Coumarans

There are a number of biologically active natural and synthetic compounds based on the 2,3-dihydrobenzofurane core (Figure 2). Coumarans demonstrate antitubercular, anti-HIV, anticancer, cytotoxic, antiprotozoal, and other activities. They are

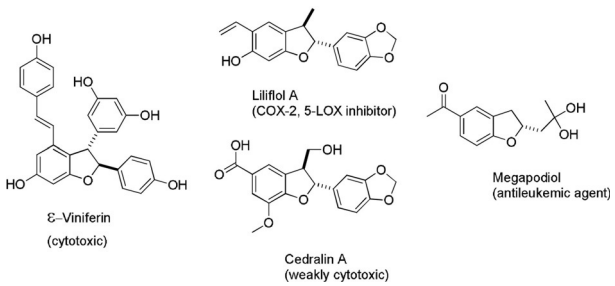
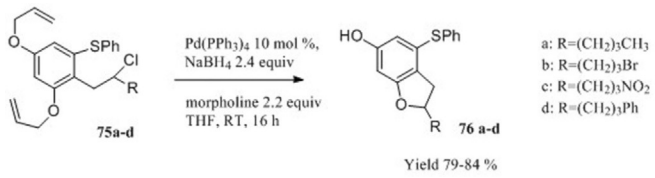


Figure 2. Coumaran-based natural compounds.

also widely used as building blocks in organic synthesis. For these reasons, the development of new and efficient synthetic approaches to such compounds has drawn much attention.

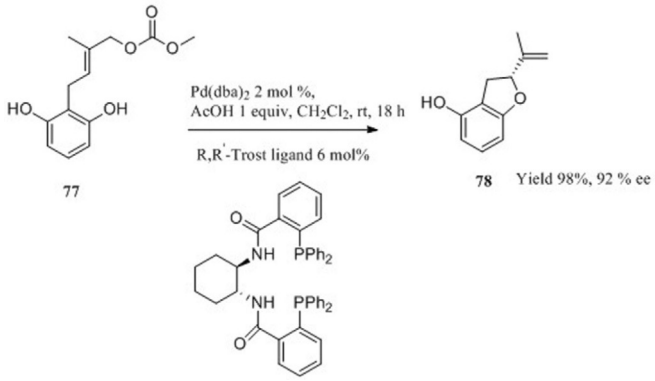
3.1. Palladium-Catalyzed Cyclization

The Pd-catalyzed deprotection of the allyl ethers in coupling products **75a–d** triggers cyclization to give important benzofuran scaffolds **76a–d**. The reaction proceeds efficiently under mild conditions with the use of $NaBH_4$ and morpholine as the allyl scavenger[63] (Scheme 32).



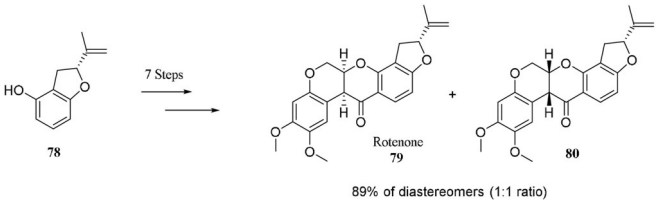
Scheme 32. Pd-catalyzed deallylation/cyclization.

In a stereoselective synthesis, the key step involves a Trost Pd π-allyl-mediated cyclization, in which (*E*)-4-(2,6-dihydroxyphenyl)-2-methyl-2-butenyl methyl carbonate (**77**) is treated with a catalytic amount of palladium in the presence of the (R,R′)-Trost ligand to afford (*R*)-2-isopropenyl-2,3-dihydrobenzofuran-4-ol (**78**) (Scheme 33).[64]



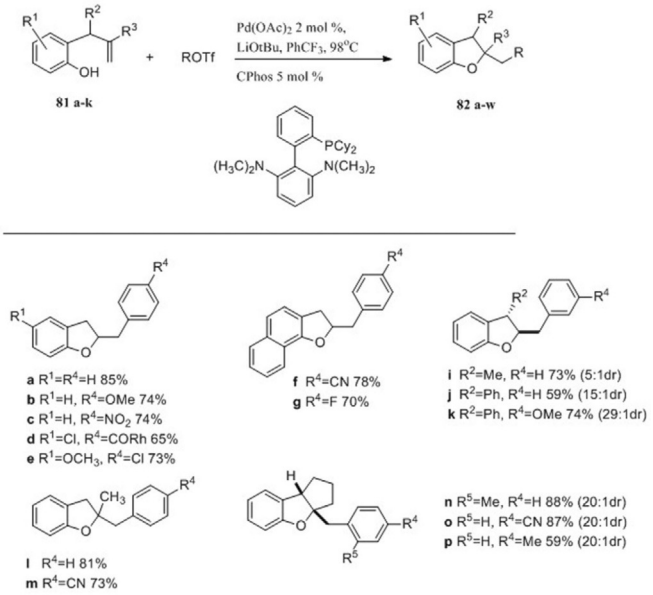
Scheme 33. Stereoselective synthesis of dihydrobenzofurans.

This asymmetric synthesis affords dihydrobenzofuran skeleton **78** with isopropenyl and phenol substituents at the 2- and 4-positions, respectively. Skeleton **78** can be used for the synthesis of the natural product rotenone (**79**) (Scheme 34), which is obtained as a 1:1 mixture with diastereomer **80** in 89% yield.



Scheme 34. Synthesis of rotenone.

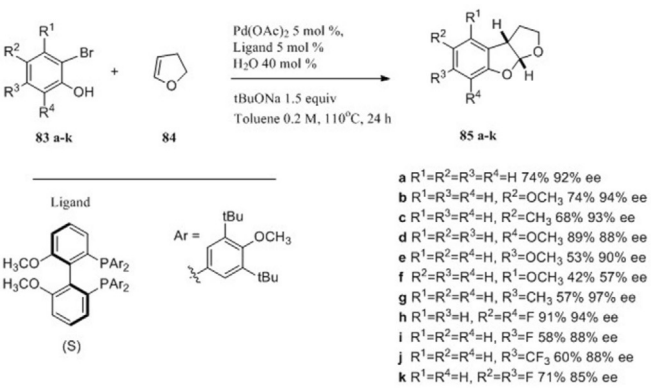
Hutt and Wolfe report a method for the synthesis of 2,3-dihydrobenzofurans **82** by the Pd-catalyzed alkene carboalkoxylation of 2-allylphenols **81**; the reaction proceeds through key anti-oxypalladation of the pendant alkene of the substrate (Scheme 35).[65]



Scheme 35. Pd-catalyzed synthesis of dihydrobenzofurans.

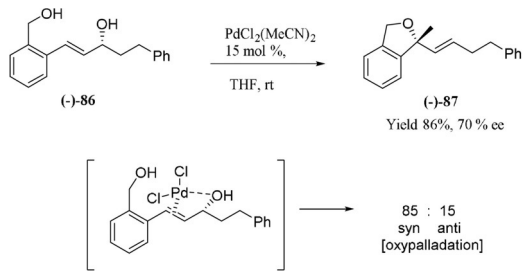
Borrajo-Calleja et al. report a method for the enantioselective Pd-catalyzed intermolecular carboetherification of dihydrofurans **84** by using bromophenol derivatives **83**. The in situ generation of a chiral bisphosphine monoxide ligand is crucial, and a general catalytic system has been identified on the basis of this approach. It provides access to fused tetrahydrofurobenzofurans **85** in consistently high yields and enantiomeric excess values (Scheme 36).[66]

Ida et al. use oxypalladation of ε-hydroxy chiral allylic alcohol **86** to synthesize **87**. In the major pathway, the chiral allylic al-



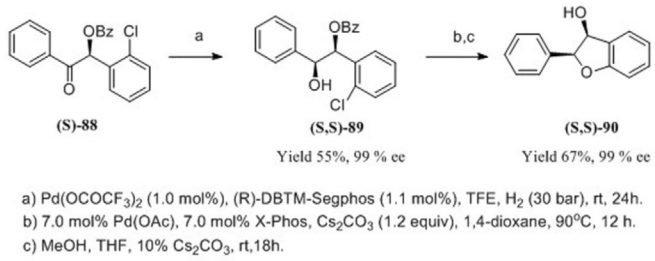
Scheme 36. Synthesis of tetrahydrofurobenzofurans.

cohol controls coordination of Pd^{II} to the *syn* face. Subsequent *syn*-oxypalladation after ligand exchange and *syn*-elimination of PdCl(OH) yields the chiral cyclic system bearing an alkene group (Scheme 37).[67]



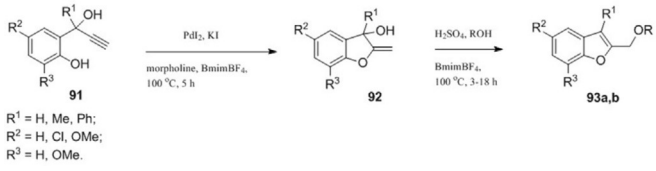
Scheme 37. Intramolecular oxypalladation of (*R*,*E*)-1-[2-(hydroxymethyl)phenyl]-5-phenylpent-1-en-3-ol.

Chen et al. use chemoselective C–O bond cleavage of the ester alkyl side chain in α-acyloxy ketone **88** for the enantioselective synthesis of (*S*,*S*)-dihydrobenzofuran derivative **90**; the reaction involves palladium-catalyzed hydrogenolysis and proceeds via *syn*-hydroxy ether **89** (Scheme 38).[68]



Scheme 38. Synthesis (*S*,*S*)-dihydrobenzofuran. Bz = benzoyl, (*R*)-DBTM-Segphos = [(4*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine], TFE = 2,2,2-trifluoroethanol, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

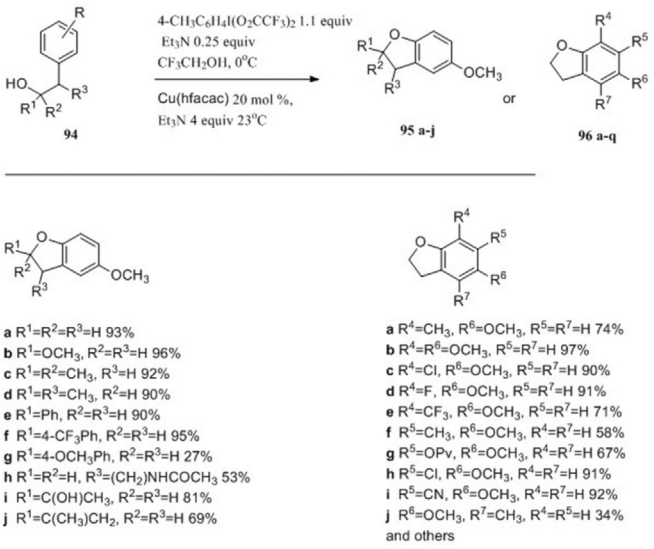
Mancuso and Gabriele present a method for the synthesis of 2-methylene-2,3-dihydrobenzofuran-3-ols **92** through the heterocyclization of 2-(1-hydroxyprop-2-ynyl)phenols **91** in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) by using a recyclable palladium catalyst (Scheme 39).[69] The authors note that this process can be conveniently performed in an ionic liquid, such as $BmimBF_4$, as the solvent and that by using this unconventional medium it is possible to recycle the catalytic system several times without any appreciable loss in activity. Furthermore, in $BmimBF_4$, methylenedihydrobenzofuranols **92** can be readily converted into 2-hydroxymethylbenzofurans **93 a** (R = H) and 2-methoxymethylbenzofurans **93 b** (R = Me) by acid-catalyzed allylic isomerization and allylic nucleophilic substitution in a one-pot fashion.



Scheme 39. Synthesis of 2-hydroxymethylbenzofurans **93 a** and 2-methoxymethylbenzofurans **93 b** by one-pot PdI_2/KI-catalyzed cycloisomerization of 2-(1-hydroxyprop-2-ynyl)phenols followed by allylic isomerization and allylic nucleophilic substitution.

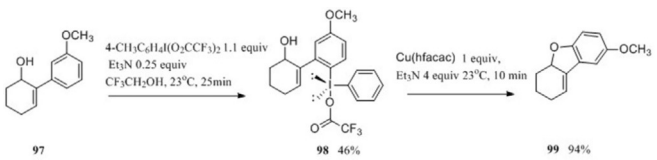
3.2. Copper-Catalyzed Cyclization

Alvarado et al. describe an alternative method for the synthesis of functionalized benzofurans and dihydrobenzofurans **95** and **96** through direct intramolecular aryl C–H bond functionalization of phenylethanols **94** under conditions mild enough to minimize oxidation of the alcohol functionality in the substrates. Optimization of the reaction conditions permits various substituents (Scheme 40).[70]



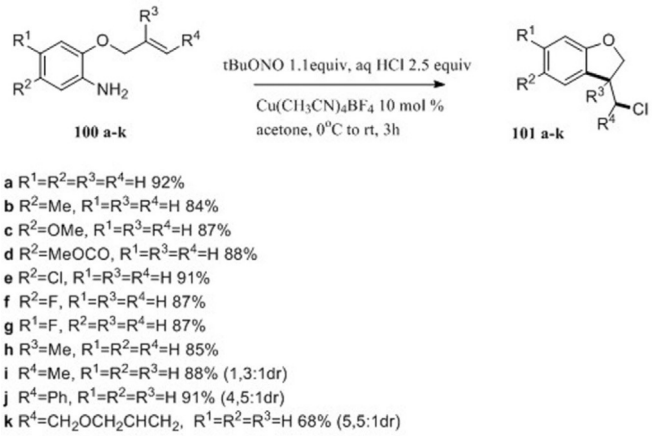
Scheme 40. Synthesis of functionalized dihydrobenzofurans. hfacac = hexafluoroacetylacetone.

Alvarado et al. also report diaryliodonium derivatives as intermediates for the synthesis of dihydrobenzofurans. To gain initial insight into the reaction mechanism, the authors perform the reaction with substrate **97** in the absence of a copper additive. After 25 min at room temperature, they report the isolation of diaryl-λ^3-iodane **98** in 46% yield. Nearly quantitative cyclization to dihydrobenzofuran **99** occurs if diaryl-λ^3-iodane **98** is treated with $Cu(hfacac)_2$ (1 equiv) and triethylamine in TFE at room temperature for 10 min (Scheme 41).[70]



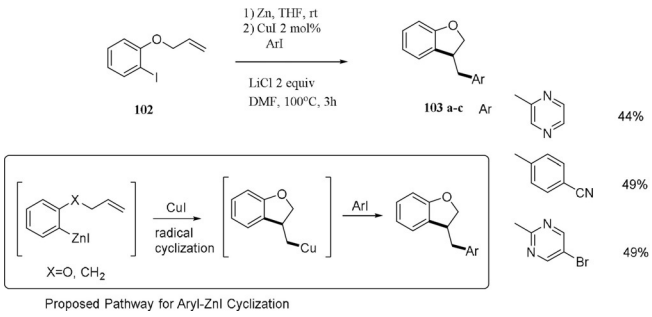
Scheme 41. Synthesis of a dihydrobenzofuran.

Ouyang et al. use copper-catalyzed radical carbochlorination or carbobromination to synthesize compounds **101**. Intramolecular cyclization occurs through aryl radicals, which are generated in situ from bench-stable aryl amines **100** by using aqueous hydrogen halides as the halogen sources (Scheme 42).[71]



Scheme 42. Radical carbochlorination for the synthesis of dihydrobenzofurans.

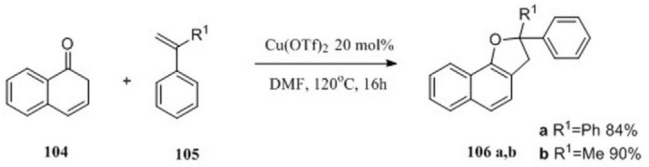
Thapa et al. propose a strategy that difunctionalizes unactivated olefins **102** in the 1,2-positions with two carbon-based entities. This method utilizes alkyl/arylzinc reagents derived from olefin-tethered alkyl/aryl halides that undergo radical cyclization to generate C(sp^3)–Cu complexes in situ, which are intercepted with aryl and heteroaryl iodides. (Arylmethyl)carbocycles and (arylmethyl)heterocycles **103** can be synthesized with this new method (Scheme 43).[72]



Scheme 43. Cyclization/coupling of arylzinc reagents.

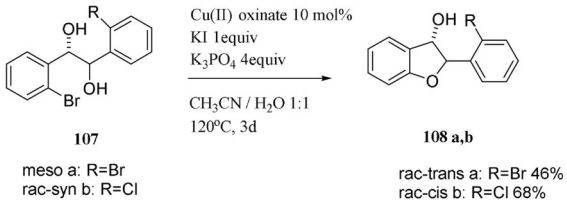
Copper-catalyzed annulation, through an oxidative free-radical process from aryl ketones **104** and aromatic olefins **105** without the use of an external oxidant, provides naphthodihydrofurans **106** from readily available starting materials. Complete regioselectivity, broad substrates scope, and wide availability of the starting materials render this protocol amenable to synthesizing a library of furan derivatives (Scheme 44).[73]

A copper-catalyzed intramolecular Ullmann coupling of *syn*-1,2-bis(2-bromoaryl)ethane-1,2-diols **107** with a catalytic



Scheme 44. Synthesis of naphthodihydrofurans.

amount of copper(II) oxinate as the copper source, K_3PO_4 as the base, and KI as the reductant in aqueous acetonitrile selectively delivers dihydrobenzofuro[3,2-b]benzofurans **108** in diastereomerically and enantiomerically pure form in yields up to 90%. The aforementioned pure form can be obtained by catalytic dihydroxylation of the corresponding (*E*)-stilbenes (Scheme 45).[74]

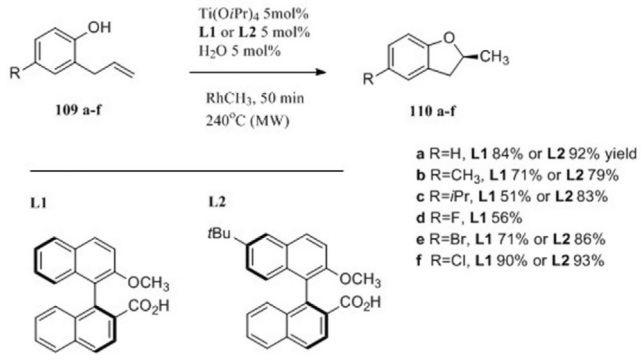


Scheme 45. Mono-O-arylation of anti-1,2-bis(2-haloaryl)ethane-1,2-diols.

3.3. Cyclization by Other Transition Metals

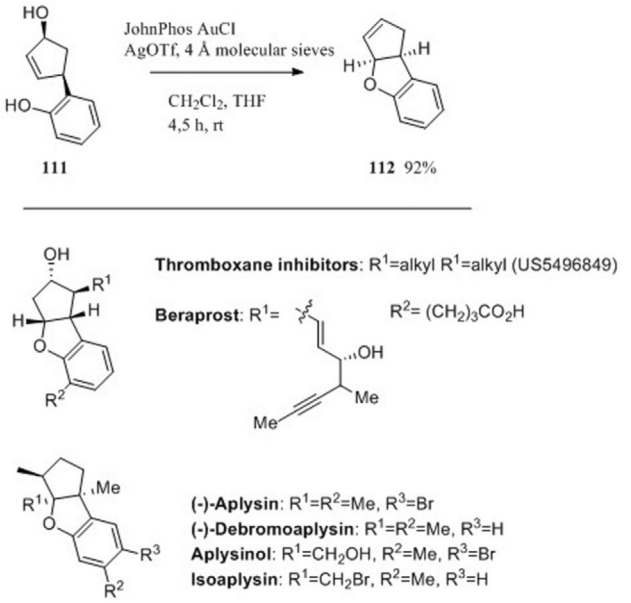
Schlîter et al. report the asymmetric hydroalkoxylation of nonactivated alkenes as examples of the cyclization of 2-allylphenols **109** to 2-methyl-2,3-dihydrobenzofurans **110**. The reaction is catalyzed by a chiral catalyst based on a titanium–carboxylate complex. The remarkably high temperature of the process exceeds those previously used in asymmetric catalysis (Scheme 46).[75]

de Oliveira Silva et al. use arylcyclopentenol **111** to construct more complex chiral scaffold **112** possessing the basic framework of many important drugs and/or bioactive natural products, such as the thromboxane inhibitor beraprost and the aplysins. Gold-catalyzed cyclization affords the corresponding fused tricyclic system in good to excellent yield and diastereo-



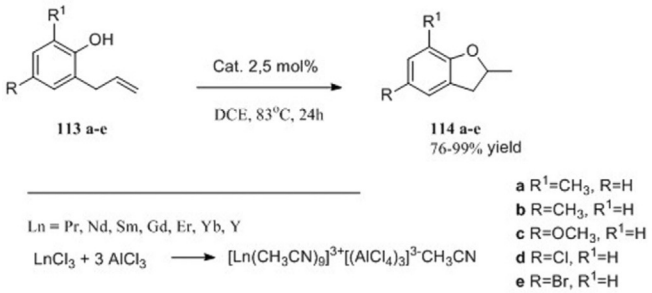
Scheme 46. Asymmetric hydroalkoxylation with titanium catalysts.

selectivity. As expected, no enantiodepletion is observed in the tricyclic product, which demonstrates the synthetic potential of the Heck–Matsuda method for the synthesis of complex chiral scaffolds (Scheme 47).[76]



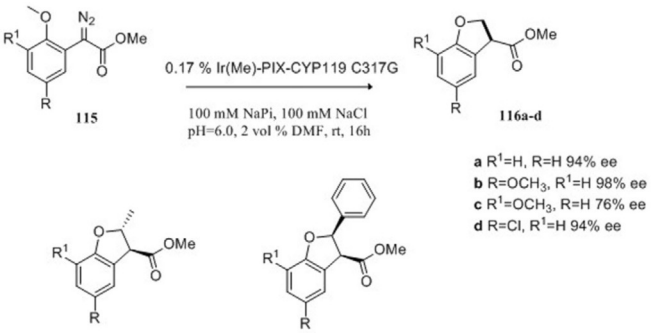
Scheme 47. Gold-catalyzed cyclization to yield fused tricyclic systems. JohnPhos = biphenyl-2-yldi-*tert*-butylphosphine.

Zhu et al. report a method for the intramolecular hydroalkoxylation/cyclization of aromatic alkenols **113** to yield 2,3-dihydrobenzofurans **114**. The reaction is catalyzed by a $[Ln(CH_3CN)_9]^{3+}[(AlCl_4)_3]^{3-}CH_3CN$ complex (Scheme 48).[77]



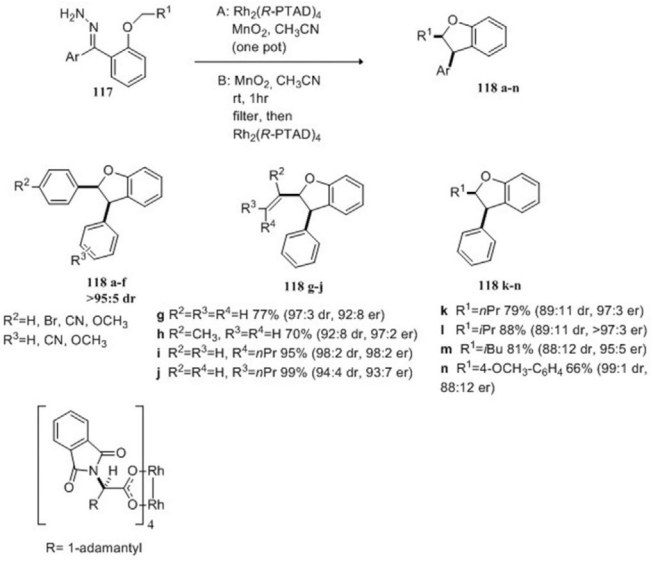
Scheme 48. Intramolecular hydroalkoxylation of unactivated alkenols.

In their report, Dydio et al. use a promising metalloenzyme approach to synthesize 2,3-dihydrobenzofurans. They prepare an artificial metalloenzyme from *Sulfolobus solfataricus* thermophile CYP119. The main goal of such catalysis is the preparative scale of the reactions, which proceed with high substrate concentrations and high turnover numbers. Thus, the described artificial metalloenzyme used for the conversion of **115** into **116**, through carbene insertion into a C–H bond, operates with high productivity under conditions suitable for preparative scale. The catalyst can be recycled four times for the formation of **116** without any loss in enantioselectivity (Scheme 49).[78]



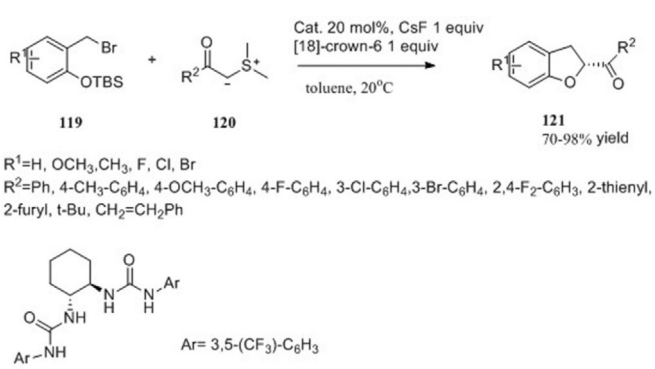
Scheme 49. Synthesis of 2,3-dihydrobenzofurans. NaPi = sodium phosphate buffer.

Soldi et al. and Lamb et al. independently report the use of rhodium-catalyzed C–H insertion reactions of donor–donor carbenoids to synthesize densely substituted benzodihydrofurans **118** with high levels of enantio- and diastereoselectivity. Unlike the reactions of metal carbenes with electron-withdrawing groups attached, attenuated electrophilicity enables these reactions to be conducted in Lewis base solvents (e.g., acetonitrile) and in the presence of water (Scheme 50). The diazo precursors for these species are prepared in situ from hydrazones **117** by using a mild and chemoselective oxidant (e.g., MnO_2).[79,80]



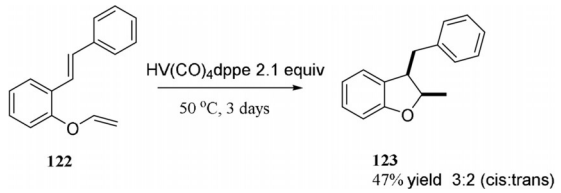
Scheme 50. Enantioselective C–H insertion reactions of substituted benzyl ethers. *R*-PTAD = (*R*)-(−)-(1-adamantyl)-(*N*-phthalimido)acetato.

Yang and Xiao report the first example of a catalytic asymmetric formal [4+1] annulation reaction between sulfur ylides **120** and *ortho*-quinone methides generated in situ from (bromomethyl)benzenes **119**. They identify a C_2-symmetric chiral urea to be the optimal H-bonding catalyst, and it affords a wide range of chiral 2,3-dihydrobenzofurans **121** in high yields (70–98%) with moderate enantioselectivities (up to 89:11 enantiomeric ratio; Scheme 51).[81]



Scheme 51. Catalytic asymmetric synthesis of chiral dihydrobenzofurans.

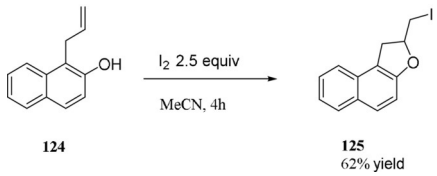
Kuo et al. detail a method for the synthesis of substituted tetrahydrofurans **123** through the 5-*exo* cyclization of α-alkoxy radicals generated by H• transfer to enol ethers **122**. This process is catalyzed by transition-metal hydrides (Scheme 52).[82]



Scheme 52. Synthesis of tetrahydrofurans catalyzed by transition-metal hydrides. dppe = 1,2-bis(diphenylphosphino)ethane.

3.4. Cyclization by Iodine

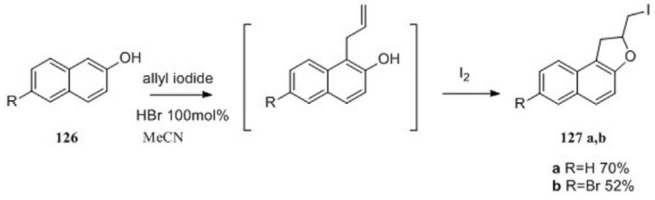
The reaction of 1-allyl-2-naphthol (**124**) with iodine yields 2-(iodomethyl)-1,2-dihydronaphtho[2,1-*b*]furan (**125**) in 62% yield through a 5-*exo*-*trig*-type iodocyclization (Scheme 53).[83]



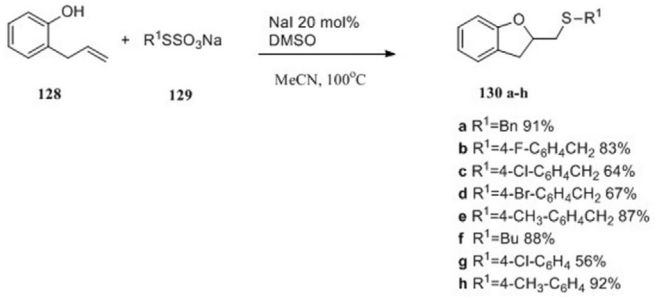
Scheme 53. Synthesis of 2-(iodomethyl)-1,2-dihydronaphtho[1,2-*b*]furan.

Xu et al. report a direct route to dihydrobenzofurans **127** through the HBr-catalyzed allylation of naphthols **126** with allyl iodide, followed by iodocyclization without isolation of the byproducts (Scheme 54).[84]

Zhang et al. outline a method for the iodine-catalyzed oxysulfenylation of alkenes **128** with various thiosulfates **129** for the efficient synthesis of sulfenylated 2,3-dihydrobenzofurans **130** and β-acetoxy sulfides. These reactions involve the use of stable, odorless, and environmentally friendly thiosulfates as thiolating reagents, DMSO as a mild oxidant, and 2-allylphenol or acetic acid as a nucleophile (Scheme 55).[85]



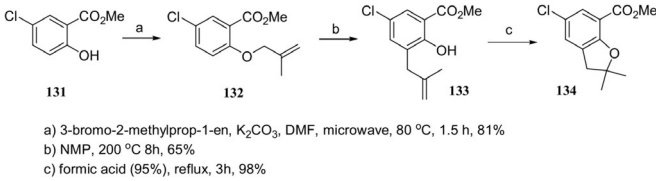
Scheme 54. HBr-mediated tandem allylation/iodocyclization for the synthesis of dihydronaphthofurans.



Scheme 55. Synthesis of sulfenylated 2,3-dihydrobenzofurans.

3.5. Acid- and Base-Catalyzed Cyclizations

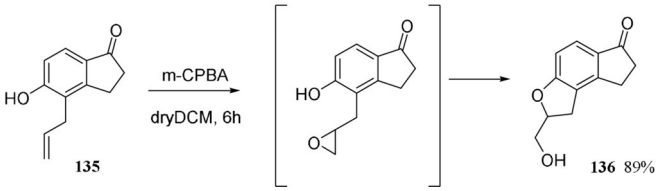
Cheng et al. synthesize **134** from **131** in three steps. The first step comprises the synthesis of **132**, which is followed by rearrangement into **133** upon heating in the presence of 1-methylpyrrolidin-2-one (NMP). Heating of **133** at reflux in 95% formic acid affords **134** in excellent yield (Scheme 56).[86]



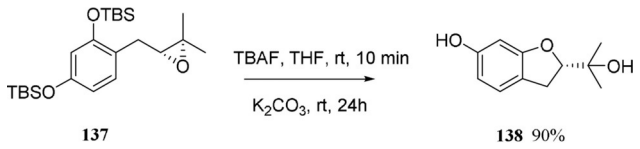
Scheme 56. Synthesis of 2,2-dimethyl-2,3-dihydrobenzofuran.

Nagarapu et al. achieve the epoxidation of **135** with *m*-chloroperbenzoic acid (*m*CPBA) to afford **136** in 89% yield. Epoxide formation and opening of the epoxide ring with a free hydroxy group occurs in a single step (Scheme 57).[87]

Base-promoted 5-*exo*-*tet* cyclization, after complete removal of the TBS groups of **137** under action of tetrabutylammonium fluoride (TBAF) and K_2CO_3, directly yields **138** in an efficient one-pot reaction (Scheme 58).[88]

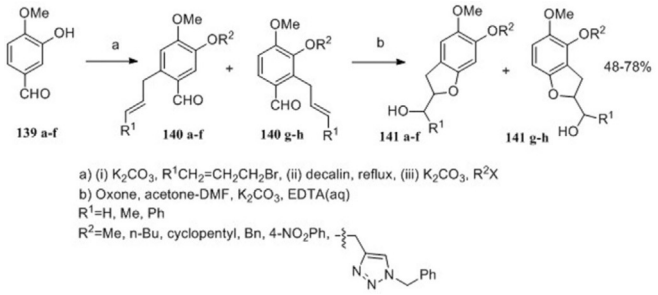


Scheme 57. Synthesis indeno[5,4-*b*]furan.



Scheme 58. Synthesis of 2-hydroxymethyl-2,3-dihydrobenzofurans.

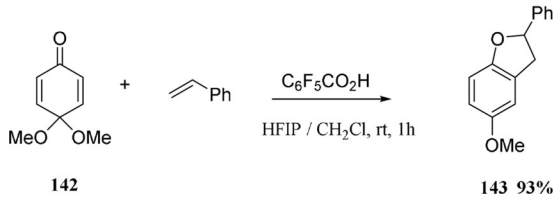
Chang et al. describe a one-pot protocol toward 2-hydroxymethyl-2,3-dihydrobenzofurans **141** starting with oxygenated benzaldehydes **139**. The facile one-pot process comprises oxidation of *o*-allylbenzaldehydes **140** with Oxone in an acetone/DMF solvent mixture in the presence of an aqueous EDTA solution, followed by intramolecular ring closure of resulting *o*-allylphenols (not shown) to give **141** in acceptable yields (Scheme 59).[89]



Scheme 59. Synthesis of **141**. EDTA = ethylenediaminetetraacetic acid.

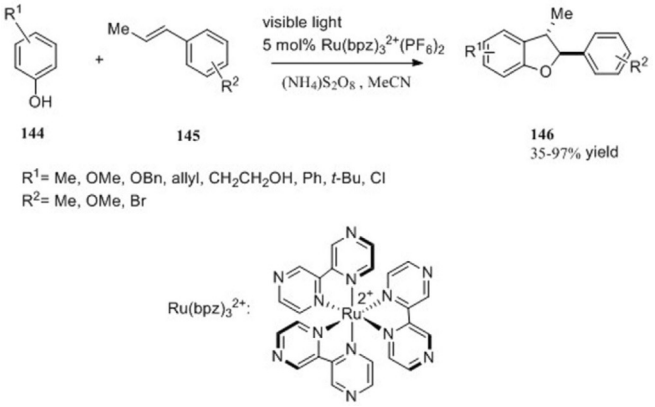
3.6. [3+2] Cycloaddition

The [3+2] coupling of **142** and alkene nucleophiles promoted by a specific Brønsted acid affords dihydrobenzofuran **143** in high yield in a solvent mixture of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and dichloromethane (Scheme 60).[90]



Scheme 60. Synthesis of 2-phenyldihydrobenzofuran from quinone monoacetal.

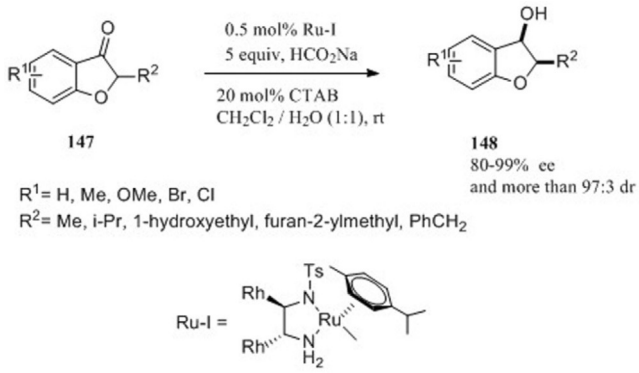
Blum et al. detail the development of a robust photocatalytic method for the oxidative [3+2] cycloaddition of phenols **144** and electron-rich styrenes **145** for the synthesis of compounds **146** in high yields. Transition-metal photoredox catalysis enables the use of ammonium persulfate as a terminal oxidant, which results in the formation of an innocuous and easily separated inorganic byproduct (Scheme 61).[91]



Scheme 61. Photocatalytic synthesis of dihydrobenzofurans by oxidative [3+2] cycloaddition.

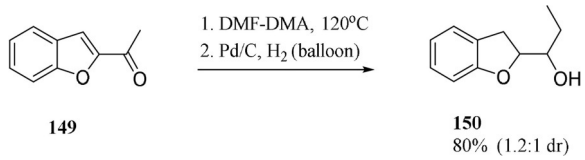
3.7. Miscellaneous

Fang et al. disclose the preparation of *cis*-2,3-dihydrobenzofuranols with two stereocenters through the aqueous asymmetric transfer hydrogenation of benzofuranones with a Ru^{II} metal catalyst by dynamic kinetic resolution. The authors transform a variety of α-alkyl benzofuranones **147** into optically pure 2,3-dihydrobenzofuran-3-ols **148** in acceptable yields with excellent enantioselectivities under mild conditions (Scheme 62).[92]



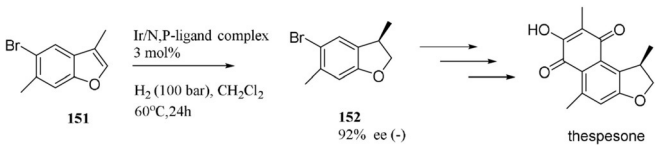
Scheme 62. Ruthenium-catalyzed synthesis of *cis*-2,3-dihydrobenzofuran-3-ols. CTAB = cetyltrimethylammonium bromide = hexadecyltrimethylammonium bromide.

Borah et al. outline the transformation of 2-acetylbenzofuran (**149**) into the corresponding enaminone followed by hydrogenation over Pd/C to afford α-methylated over-reduced product **150** in 80% yield as a 1.2:1 mixture of diastereomers (Scheme 63).[93]



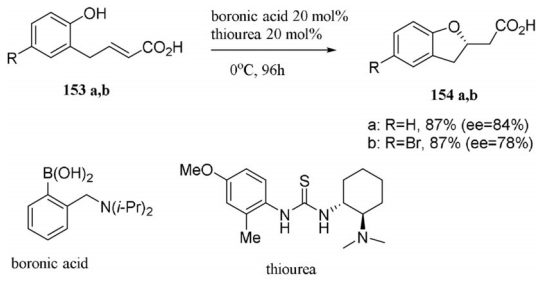
Scheme 63. Synthesis 2-hydroxymethyl-2,3-dihydrobenzofurans. DMA = dimethylacetamide.

Pauli et al. describe the hydrogenation of 2- and 3-substituted furans by using iridium catalysts that bear bicyclic pyridine–phosphinite ligands. They use the asymmetric hydrogenation of 3-methylbenzofuran derivative **151** to give (*R*)-5-bromo-3,6-dimethyl-2,3-dihydrobenzofuran (**152**) as a key step in the formal total synthesis of the cytotoxic naphthoquinone natural product (−)-thespesone (Scheme 64).[94]



Scheme 64. Asymmetric hydrogenation of benzofuran.

Azuma et al. use a bifunctional aminoboronic acid to facilitate the intramolecular oxa-Michael reactions of α,β-unsaturated carboxylic acids **153**. The combination of an arylboronic acid with a chiral aminothiourea allows these reactions to proceed in an enantioselective manner to afford compounds **154** in high yields with high enantioselectivities (up to 96% *ee*; Scheme 65).[95]

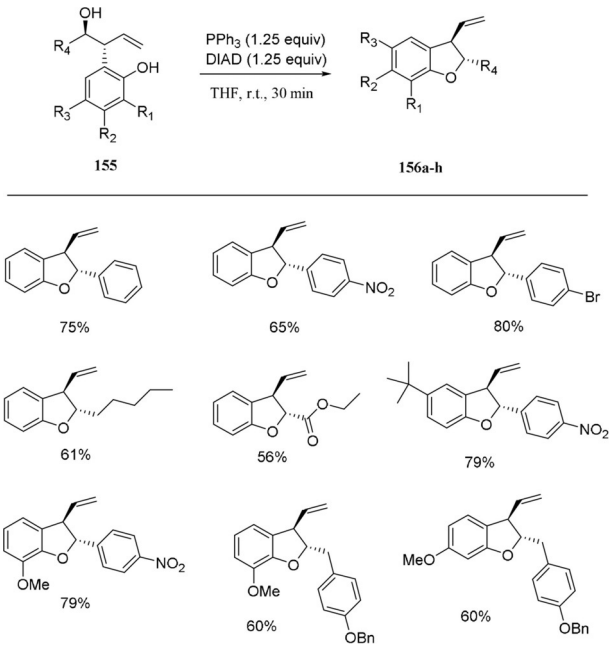


Scheme 65. Intramolecular hetero-Michael reaction of α,β-unsaturated carboxylic acids for the synthesis of benzofurans.

Hemelaere et al. recount the use of a cross-metathesis/isomerization/allylboration sequence followed by an intramolecular Mitsunobu process for the diastereoselective synthesis of *trans*-2,3-disubstituted dihydrobenzofurans **156** from diols **155** (Scheme 66).[96]

4. Conclusions

In this review, we described recent advances in the chemistry of phthalans and coumarans. Presented methods for the synthesis of these cores include transition-metal-catalyzed cycloadditions, metal-free cycloadditions, Diels–Alder reactions, Garratt–Braverman cyclizations, transformations of phthalides, transformations of furans, transformations of indolines, and cyclizations of diols. Although many of the mentioned recent developments in the preparation of phthalans and coumarans are based on readily available starting materials and provide high yields, there is a lack of methods allowing the synthesis of stereochemically pure compounds. Further work towards the development of such synthetic strategies will increase the potential of compounds built on the basis of phthalan and coumarin scaffolds as perspective compounds for the treatment of various diseases.



Scheme 66. Synthesis of 2-vinyldihydrobenzofurans. DIAD = diisopropyl azodicarboxylate.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalysis · cyclization · cycloaddition · oxygen heterocycles · synthetic methods

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