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 chemos- 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 furuquinocines are antibiotics.[13] Other derived compounds exhibit cytotoxic and antiprotzoal 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 indoles. 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, anti-fungal, 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.](image-url)
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-diyynes 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 \( 3b \). 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 \( 4 \) with 1,6-diyynes \( 1^{[22]} \) (Scheme 3). Along with \( \text{Cp}^*\text{Ru}(\text{cod}) \), \( \{\text{Rh}(\text{cod})_2\}B\text{F}_4/\text{BINAP} \) 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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cobalt is effective for the [2+2+2] cycloaddition of 1,6-diyne 1 and various substituted alkynes 6 (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.

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.

In 2016, Matousova et al.\[26\] investigated the cycloaddition of 1-cyclopropyl-1,6-diynes 10 with terminal alkynes 11a–f catalyzed by Wilkinson’s catalyst [RhCl(PPh3)3], Rh(cod)BF4/BINAP, CpCo(CO)3 (Cp=η5-pentamethylcyclopentadienyl), and NiBr2(PPh3)3/Zn to prepare phthalans 12a and 12b. They report that isomers 13a and 13b are formed in 4–26 % yield (Scheme 6).

Along with acetylenes in [2+2+2]-cycloaddition reactions, other 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 %.

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.
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\(^{23}\) to give 1,3-dihydroiso-
benzofurans 23 (Scheme 9).

\[
\begin{align*}
\text{Ph} & + \text{Ph} \\
& \text{condition} \rightarrow \\
& \text{DMF, 140 °C} \\
& \text{Yield 15%}
\end{align*}
\]

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-alkadiynyllic carbonates 24 with allenes 25 bearing a carbon nucleophile (Scheme 10).

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-dihydroisobenzofurans 31 through the palladium-catalyzed domino carbopalladation of bromoenynes 29 and internal alkynes 30\(^{32}\) (Scheme 12).

A plausible mechanism involves the formation of \(\text{Pd}^0\) from \(\text{Pd}^{II}\) by reducing \(\text{PPh}_3\), which enters the catalytic cycle by oxidative addition to the \(\text{C}(\text{sp}^2)\)-Br bond of bromoynne 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 \(\beta\)-dehydropalladation sequence.

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).

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 dicyclopentene 36 with the
molecular Diels–Alder cycloaddition. This reaction requires \( \text{Co(OAc)}_2 \) 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 ZnI₂ as a Lewis acid is required to activate the catalyst.

Tigchelaar et al. disclose an investigation into the intramolecular [4+2] cycloadditions of diene-tethered alkynyl halides catalyzed by iridium, specifically with the use of \( [\text{IrCl(cod)}]_2 \) or \( \text{IrCl(CO)}(\text{PPh}_3)_2 \) as the catalyst and \( \text{PPh}_3 \) 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.

### 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 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 KOtBu 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.](image-url)
In 2015, Shibuya et al. reported a combined transition-metal-catalyzed and photo-promoted process for preparing hetero-fused phthalans (Scheme 22). In their report, they show that the first hydrocarboxylative cyclization of 1,7-diaryl-1,6-diynes is optimized for the highly stereoselective formation of exocyclic dienyl acetates by using the \([\text{Cp}^*\text{RuCl(-cod)}]\) catalyst with \(\text{Bu}_4\text{NCl}\) as an additive. Subsequent oxidative photocyclization of the resulting exocyclic dienyl acetates efficiently affords desired 2,3-fused 4-phenylnaphthalen-1-yl acetates if the reaction is performed with \(\text{I}_2\) in a mixed solvent of toluene and THF.

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 (Scheme 23). Phthalans are synthesized in a one-pot protocol in 51–62% yield from ether and corresponding halogenated aryls via alkynyl ethers.

Zhou et al. delineate Selectfluor-promoted sequential reactions to produce fused polycyclic skeletons via allene intermediates by a metal-free construction (Scheme 24). The reactions are performed by using \(\text{C}_6\text{H}_4\text{Cl}_2\) (0.2 mmol) and Selectfluor (0.22 mmol) in \(\text{CH}_2\text{Cl}_2\) (2.5 mL) at room temperature or in toluene (2.5 mL) under a \(\text{N}_2\) atmosphere at 80 °C.

2.3. Transformation of Furans into Phthalans

Scheme 25 shows the general transformation of furans into phthalans. Typical reaction conditions include the use of a gold-based catalyst and a chlorine-containing solvent, such as \(\text{CHCl}_3\) or \(\text{CH}_2\text{Cl}_2\), 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.

2.4. Cyclization of Diols

Tonachini et al. report an interesting synthetic protocol for phthalans. The reaction of 1,4-diol with dimethyl carbonate (DMC) in the presence of a base (\(\text{NaOMe}\)) under mild conditions leads to corresponding phthalan in high yields within a short reaction time (Scheme 26).
2.5. Transformation of Indolines

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

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 recylization 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 presented an interesting approach toward phthalans from phthalides through Fe-catalyzed hydrosilylation (Scheme 29).

In 2015, the Beller group also reported the ruthenium(II)-catalyzed formation of phthalans from bromophthalide promoted by a Lewis acid through selective hydrogenation (Scheme 30).

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 is presented by Mancuso. 3-[(Alkoxycarbonyl)methylene]isobenzofuran-1(3H)-imines are selectively obtained if the oxidative carbonylation of 2-alkynylbenzamides, 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 alkoxy carbonylation.

Scheme 31. Synthesis of 3-[(alkoxy carbonyl)methylene]isobenzofuran-1(3H)-imines by the Pd(II)-catalyzed O-heterocyclization/alkoxycarbonylation of 2-alkynylazabenamides.

3. Synthetic Routes to Coumarans

There are a number of biologically active natural and synthetic compounds based on the 2,3-dihydrobenzofuran core (Figure 2). Coumarans demonstrate antitubercular, anti-HIV, anticancer, cytotoxic, antiprotozoal, and other activities. They are...
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 benzo-furan scaffolds 76a–d. The reaction proceeds efficiently under mild conditions with the use of NaBH₄ 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-dihydroxy-phenyl)-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.

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 tetrahydrofurubenzofurans 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 34. Synthesis of rotenone.

Scheme 36. Synthesis of tetrahydrofurubenzofurans.
cohol controls coordination of Pd\textsuperscript{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).\textsuperscript{[67]}

$$\text{Scheme 37. Intramolecular oxypalladation of (R,E)-1-[2-(hydroxymethyl)phenyl]-5-phenylpent-1-en-3-ol.}$$

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

$$\begin{align*}
\text{(S,S)-88} &\xrightarrow{a} \text{OH} & \xrightarrow{b,c} \text{OH} \hspace{1cm} (S,S)-90 \\
\text{Yield 55\%}, 99\% \text{ ee} &\xrightarrow{a} \text{OH} & \xrightarrow{b,c} \text{OH} \\
\text{Yield 67\%}, 99\% \text{ ee}
\end{align*}$$

\text{Scheme 38. Synthesis of (S,S)-dihydrobenzofuran. Bz = benzoyl, (R)-DBTM-Segphos = [(4R)-(4,4'-bi-1,3-benzodioxole)-5,5'-dibis(3,5-di-tert-butyl-4-methoxyphenyl)phospine], 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 theionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (BmimBF\(_4\)) by using a recyclable palladium catalyst (Scheme 39).\textsuperscript{[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\(_4\), methylenedihydrobenzofuranos \(92\) can be readily converted into 2-hydroxydihydrobenzofuranos \(93\) \(a (R=H)\) and 2-methoxydihydrobenzofuranos \(93\) \(b (R=Me)\) by acid-catalyzed allylic isomerization and allylic nucleophilic substitution in a one-pot fashion.

3.2. Copper-Catalyzed Cyclization

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

$$\text{Scheme 40. Synthesis of functionalized dihydrobenzofuranos. hfacac = hexafluoroacetylacetone.}$$

Alvarado et al. also report diarylidoionium derivatives as intermediates for the synthesis of dihydrobenzofuranos. 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-\(\lambda^3\)-iodane \(98\) in 46% yield. Nearly quantitative cyclization to dihydrobenzofuran \(99\) occurs if diaryl-\(\lambda^3\)-iodane \(98\) is treated with Cu(hfacac)\(_2\) (1 equiv) and triethylamine in TFE at room temperature for 10 min (Scheme 41).\textsuperscript{[70]}

$$\text{Scheme 41. Synthesis of a dihydrobenzofuran.}$$
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).\textsuperscript{[71]}

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\textsuperscript{3})–Cu complexes in situ, which are intercepted with aryl and heteroaryl iodides. (Arylmethyl)carbo- and (arylmethyl)heterocycles 103 can be synthesized with this new method (Scheme 43).\textsuperscript{[72]}

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).\textsuperscript{[73]}

A copper-catalyzed intramolecular Ullmann coupling of syn-1,2-bis(2-bromoaryl)ethane-1,2-diols 107 with a catalytic amount of copper(II) oxinate as the copper source, K\textsubscript{3}PO\textsubscript{4} as the base, and KI as the reductant in aqueous acetone 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).\textsuperscript{[74]}

3.3. Cyclization by Other Transition Metals

Schäfer et al. report the asymmetric hydroalkoxylation of non-activated 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).\textsuperscript{[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 alypsins. Gold-catalyzed cyclization affords the corresponding fused tricyclic system in good to excellent yield and diastereo-
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).\[76\]

Zhu et al. report a method for the intramolecular hydroalkoxylation/cyclization of aromatic alkenols to yield 2,3-dihydrobenzofurans. The reaction is catalyzed by a \([\text{Ln}(\text{CH}_3\text{CN})_3]^{3+} \cdot [\text{AlCl}_3]^{3-} \cdot \text{CH}_3\text{CN} \) complex (Scheme 48).\[77\]

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).\[78\]

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 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 by using a mild and chemoselective oxidant.\[79,80\]

Yang and Xiao report the first example of a catalytic asymmetric formal [4+1] annulation reaction between sulfur ylides and *ortho*-quinone methides generated in situ from (bromomethyl)benzenes. They identify a \(\text{C}_2\)-symmetric chiral urea to be the optimal H-bonding catalyst, and it affords a wide range of chiral 2,3-dihydrobenzofurans in high yields (70–98%) with moderate enantioselectivities (up to 89:11 enantiomeric ratio; Scheme 51).\[81\]
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]

3.4. Cyclization by Iodine

The reaction of 1-allyl-2-naphthol (124) with iodine yields 2-(iodomethyl)-1,2-dihydronaphtho[1,2-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]

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

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). [85]

Nagarapu et al. achieve the epoxidation of 135 with m-chloroperbenzoic acid (mCPBA) 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). [86]

Base-promoted 5-exo-tet cyclization, after complete removal of the TBS groups of 137 under action of tetrabutylammonium fluoride (TBAF) and K$_2$CO$_3$, directly yields 138 in an efficient one-pot reaction (Scheme 58). [87]
Chang et al. describe a one-pot protocol toward 2-hydroxymethyl-2,3-dihydrobenzofurans starting with oxygenated benzaldehydes. The facile one-pot process comprises oxidation of o-allylbenzaldehydes 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).

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).

Blum et al. detail the development of a robust photocatalytic method for the oxidative [3+2] cycloaddition of phenols and electron-rich styrenes 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).

3.7. Miscellaneous

Fang et al. disclose the preparation of cis-2,3-dihydrobenzofuran-1-ols with two stereocenters through the aqueous asymmetric transfer hydrogenation of benzofuranones with a Ru metal catalyst by dynamic kinetic resolution. The authors transform a variety of α-alkyl benzofuranones into optically pure 2,3-dihydrobenzofuran-3-ols 148 in acceptable yields with excellent enantioselectivities under mild conditions (Scheme 62).

Borah et al. outline the transformation of 2-acetylbenzofuran into the corresponding enamino 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).
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]

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]

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, Garrett–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.

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Conflict of Interest

The authors declare no conflict of interest.

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

[1] G. Donadio, C. Sarcinelli, E. Pizzo, E. Notomista, A. Pezzella, C. Di Cristo, F. De Lise, A. Di Donato, V. Izzo, PLoS ONE 2015, 10, e0124427.
[2] J. Waugh, K. L. Goa, CNS Drugs 2003, 17, 343–362.
[3] P. Zhang, G. Cyriac, T. Kopagit, Y. Zhao, J. A. Javitch, J. L. Katz, A. H. Newman, J. Med. Chem. 2010, 53, 6112–6121.
[4] P. Bhattacharya, K. Senapati, K. Chattopadhyay, S. M. Mandal, A. Basak, RSC Adv. 2015, 5, 61562–61574.
[5] S. Rochat, T. M. Swager, J. Am. Chem. Soc. 2013, 135, 17703–17706.
[6] A.-F. Tran-Van, E. Huxol, J. M. Basler, M. Neuburger, J.-J. Adzijian, C. P. Ewels, H. A. Wegner, Org. Lett. 2014, 16, 1594–1597.
[7] R. P. Tripathi, A. K. Yadav, A. Ajay, S. S. Bisht, V. Chaturvedi, S. K. Sinha, Eur. J. Med. Chem. 2010, 45, 142–148.
[8] S. Prado, H. Ledeit, S. Michel, M. Koch, J. C. Darbord, S. T. Cole, F. Tilquin, P. Brodin, Bioorg. Med. Chem. 2006, 14, 5423–5428.
[9] B. R. Copp, Nat. Prod. Rep. 2003, 20, 535–557.
[10] Z. Xu, J. Guo, Y. Yang, M. Zhang, M. Ba, Z. Li, Y. Cao, R. He, M. Yu, H. Zhou, X. Li, X. Huang, Y. Guo, C. Guo, Eur. J. Med. Chem. 2016, 123, 309–316.
[92] L. Fang, S. Liu, L. Han, H. Li, F. Zhao, *Organometallics* 2017, 36, 1217 – 1219.

[93] A. Borah, L. Goswami, K. Neog, P. Gogoi, *J. Org. Chem.* 2015, 80, 4722 – 4728.

[94] L. Pauli, R. Tannert, R. Scheil, A. Pfaltz, *Chem. Eur. J.* 2015, 21, 1482 – 1487.

[95] T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma, Y. Takemoto, *Org. Lett.* 2014, 16, 4256 –4259.

[96] R. Hemelaere, F. Carreaux, B. Carboni, *Eur. J. Org. Chem.* 2015, 2470 – 2481.

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