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Recent Advances in the Synthesis of Dibenzofurans

Mouad Alami^a, Olivier Provot^{*a}

This review reports recent accesses to the dibenzofuran nucleus described in the literature since 2008. This article starts with synthesizing dibenzofurans by creating the C–O bond of the furan ring. In the following section, we evoke the formation of dibenzofurans by cyclizing diarylether derivatives. The last part of this update concerns the construction of dibenzofurans from benzofuran or phenol derivatives. Representative examples showing the scope of these processes illustrate new approaches and biological activities of dibenzofurans. Reaction mechanisms explaining certain dibenzofuran formation are described, as suggested by their authors.

1. INTRODUCTION.

The dibenzofuran nucleus is a tricyclic system resulting from the fusion of a benzofuran and a benzene ring in which the C2 and C3 atoms of the benzofuran are linked to the benzene ring. This class of aromatic heterocycle has received much attention from the

scientific community in recent years, as the dibenzofuran ring is present in many biologically active compounds of natural or synthetic origin,^{1,2} (Figure 1) and more recently, in organic semiconductors such as light-emitting diodes.³

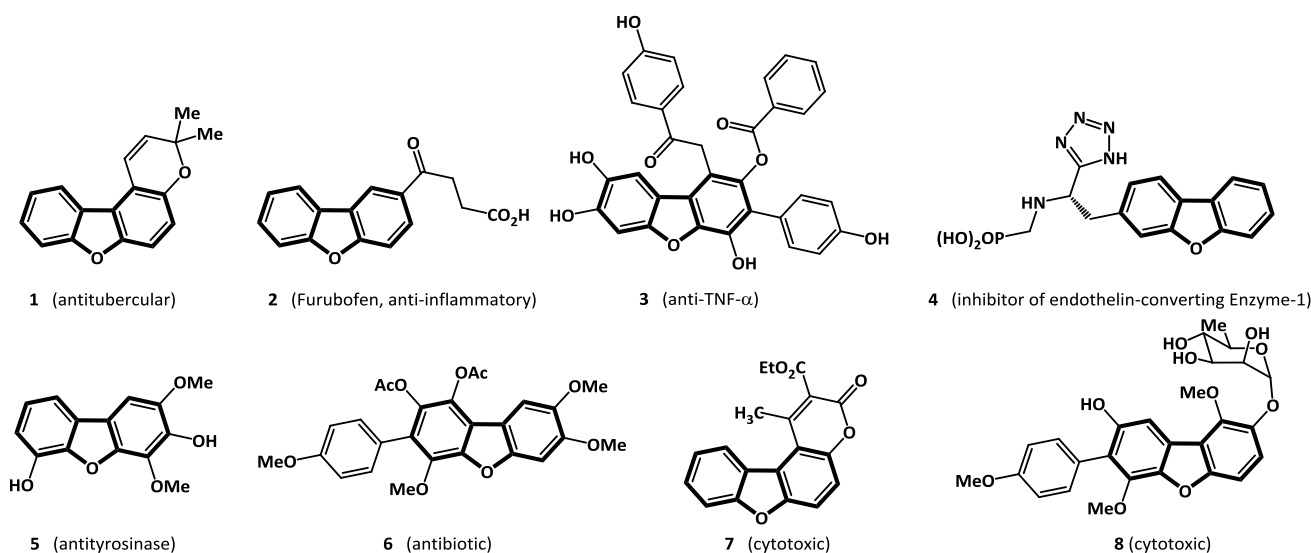


Figure 1. Biologically active dibenzofurans and derivatives.

After a brief introduction of the pathways leading to the dibenzofuran skeleton described before 2008, this review presents recent accesses to this motif. Section 2 and Section 3 concern dibenzofurans prepared by forming the C–O bond and the C–C bond of the furan ring and Section 4 evokes processes forming this tricyclic nucleus from benzofuran or phenol derivatives. More specifically, Section 2 deals with the formation of dibenzofurans by creating the C–O bond according to a C–H activation using palladium and copper catalysis followed by cyclization of resulting 2-arylphenols. Then, we mention the cycloetherification reactions of phenols having internal leaving groups as halogens, formates, molecular nitrogen, nitro-, methoxy, and B(Pin)-substituents. In

Section 3, dedicated to the syntheses of dibenzofurans by forming the C–C bond of the furan ring, we evoke successively CH–CH oxidative processes, C–H arylation reactions using various internal leaving groups and creation of the C–C bond involving a cleavage of a C–C bond as a decarboxylation for example followed by a cyclization reaction. Section 4 presents a few approaches recently developed to access the dibenzofuran motif by creating the benzene ring contiguous to the benzofuran using cyclization reaction (Diels-Alder, 6π -electrocyclization, and others). We next evoke syntheses of poly-substituted dibenzofurans from functionalized phenols according to cycloaddition reactions, electrocyclization, and Michael additions.

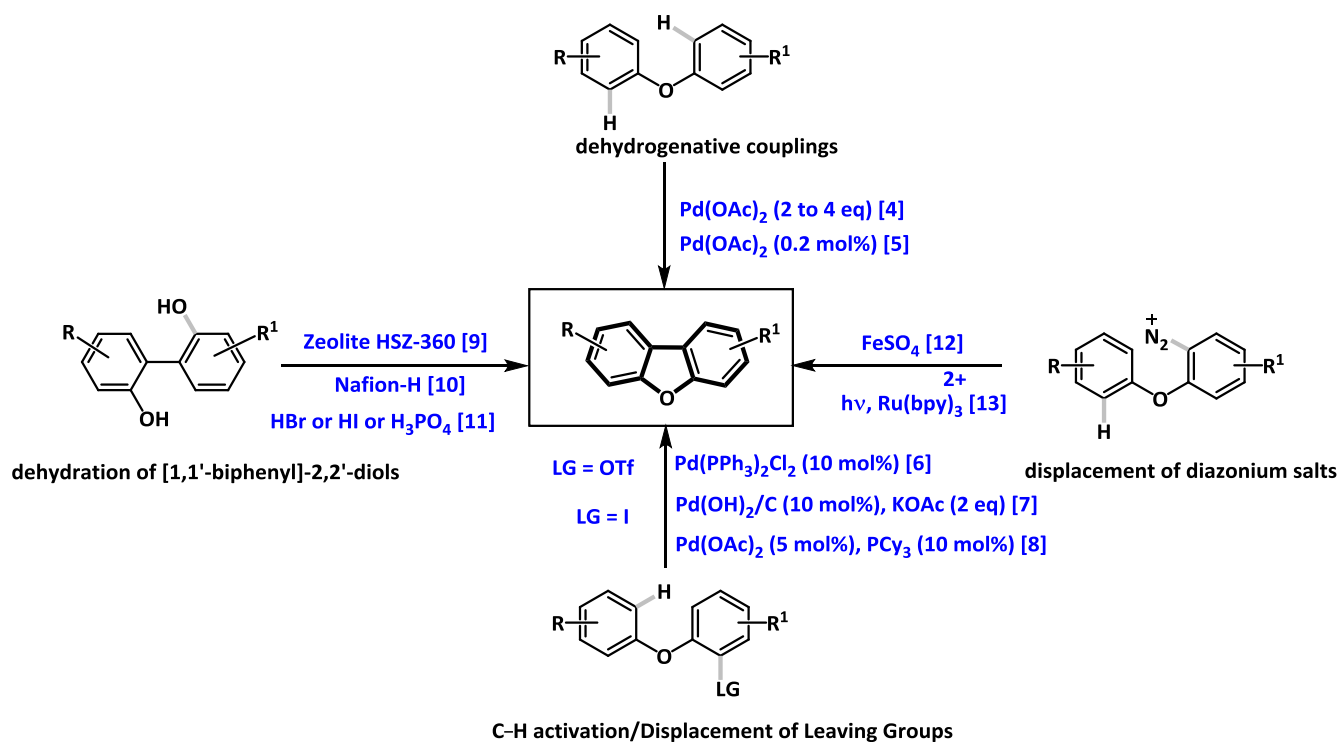


Figure 2. Representative methodologies reported before 2008 to synthesize dibenzofurans.

In this review, we present for each protocol a selection of representative examples showing the scope of these novel methodologies and the properties of some biologically active dibenzofurans.

Before 2008, there was only a few reported synthetic approaches (Figure 2) to the dibenzofuran motif despite the occurrence of this nucleus in many natural and synthetical products of interest.

Akermark proposed an intramolecular cyclization of diphenyl ethers into dibenzofurans by using $\text{Pd}(\text{OAc})_2$ in significant excess (from 2 to 4 eq) in acidic solvents.⁴ One year later, Shiotani reduced the quantity of $\text{Pd}(\text{OAc})_2$ to 0.2 mol% by using acetylacetonate (0.2 mol%) as an additive in ethyleneglycol in a rocking autoclave containing O_2/N_2 (1:1) at 150 °C.⁵ In 2002, Harvey cyclized diphenylethers and phenylnaphtylethers having on *ortho*-position a triflate ester as leaving group (LG) using $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (10 mol%), LiCl, and DBU in dry DMF at 145 °C.⁶ In 2005, Fagnou showed the efficiency of $\text{Pd}(\text{OH})_2/\text{C}$ (10 mol%) and KOAc (2 eq) to promote, in hot DMA (140 °C), the cyclization of diphenylethers having an iodine atom on the *ortho*-position.⁷ At the same time, Larock reported that this type of cyclization worked well with $\text{Pd}(\text{OAc})_2$ (5 mol%) and PCy_3 as the ligand (10 mol%).⁸ In this work, Larock obtained dibenzofurans in high yields *via* a cross-coupling reaction between *ortho*-iodophenols and silylaryltriflates followed, in the same pot, by a Pd-catalyzed cyclization. Dehydration of robust [1,1'-biphenyl]-2,2'-diols to dibenzofuran was achieved with success by using harsh acidic acid conditions such as zeolite HSZ-360,⁹ Nafion-H,¹⁰ HBr, HI and H_3PO_4 .¹¹ Wassmundt and Pedemonte proposed in 1995 the first synthesis of dibenzofurans in a Pschorr reaction by displacing 2-phenoxy-benzenediazonium salts with FeSO_4 as a radical source (6 examples; 77-83%).¹² Cano-Yelo and Deronzier also studied the synthesis of dibenzofurans by photocatalysis using diazonium salts and $\text{Ru}(\text{bpy})_3^{2+}$. They observed that this process occurred with a low yield and a slow rate.¹³ It is helpful to report the evolution of

dibenzofuran syntheses, which must now be environmentally friendly and tolerant of functional groups.

2. SYNTHESIS OF DIBENZOFURANS BY CREATING THE C–O BOND OF THE FURAN RING.

2.1 Metal-catalyzed C–H activation and C–O cyclization of 2-arylphenols (Figure 3).

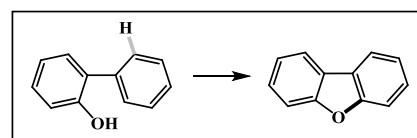
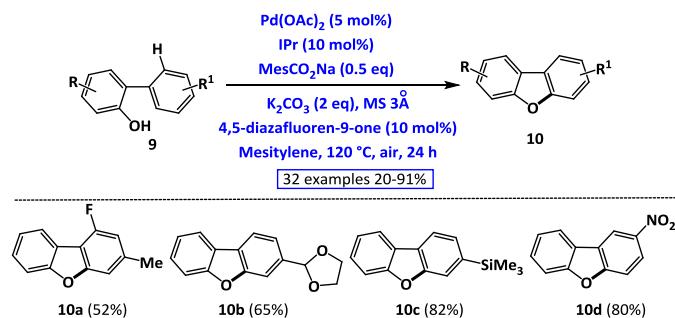


Figure 3.

2.1.1 Pd(II)-catalysis.

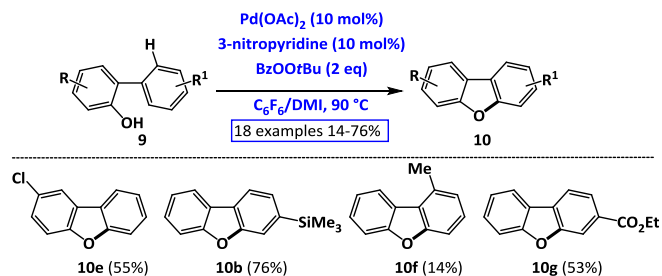
In 2011, Liu reported the first synthesis of dibenzofurans according to a C–H activation/C–O cyclization of 2-arylphenols under Pd-catalysis using air as a mild oxidant (Scheme 1).¹⁴ This work is of great significance as it was the first work concerning a preliminary C–H activation followed by a C–O bond formation in constructing dibenzofurans.



Scheme 1. Synthesis of dibenzofurans **10** from the cyclization of 2-arylphenols **9** under Pd-catalysis and air.

The authors tested a variety of weak oxidants (Cu(OAc)₂, AgOAc, and benzoquinone) to avoid the destruction of phenol derivatives in the presence of Pd(OAc)₂ and IPr ligand, but none of them was efficient. The authors finally discovered that air was efficient as the oxidizing agent. Best conditions for the cyclization of 2-arylphenols required the use of Pd(OAc)₂ as the catalyst, IPr as the ligand, K₂CO₃ as the base, MesCO₂Na as an additive and air in hot mesitylene. The reaction tolerated electron-donating (EDG) and electron-drawing (EWG) groups on both aromatic rings, leading to dibenzofurans with good to excellent yields with excellent regioselectivity (e.g. **10d**). The authors also demonstrated that dibenzofurans were prepared directly from (2-hydroxyphenyl)boronic acids. In the presence of the palladium catalyst, a coupling reaction with arylhalides occurred to give the crude phenols, which gave dibenzofurans after cyclization. This methodology applied to anilines led to the formation of carbazole derivatives according to a C–H activation/C–N cyclization.

In 2011, Yoshikai reported an alternative to this reaction by using 3-nitropyridine as the Pd(OAc)₂ ligand and *tert*-butyl peroxybenzoate (BzOOTBu) as an inexpensive oxidant (Scheme 2).¹⁵

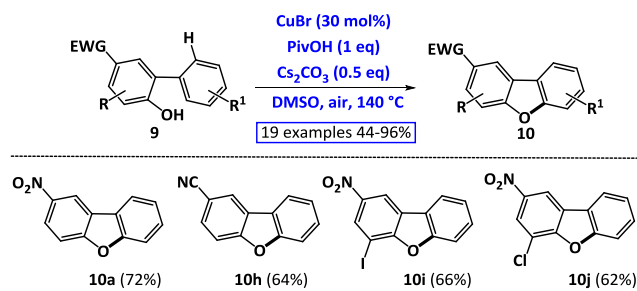


Scheme 2. Synthesis of dibenzofurans **10** from the cyclization of 2-arylphenols **9** using Pd(OAc)₂ and 3-nitropyridine.

If yields were moderate, the main advantage of this protocol is its practicality using a pyridine ligand and an inexpensive oxidant in a mixture of C₆F₆ and *N,N'*-dimethyl-imidazolinone (DMI). Schmidt and Riemer in 2017 considerably accelerated the reaction time of this reaction achieved with the same reagents by using DME as the solvent and microwave activation at 150 °C.¹⁶ However, these cyclizing operating conditions did not work in preparing dibenzofurans from (2-hydroxyphenyl)boronic acids and aromatic halides in a one-pot process, because the base used in the Suzuki coupling, usually K₂CO₃, prevented the final cyclization step.

2.1.2 Cu(I)- and Cu(II)-catalysis.

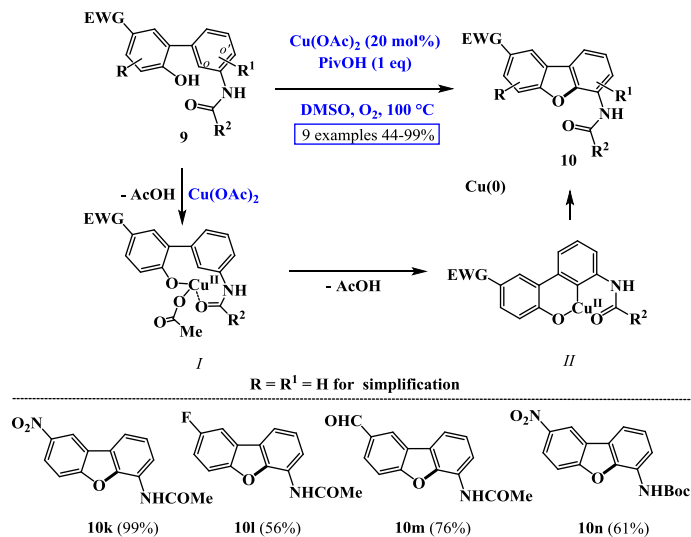
In 2012, Zhu proposed to prepare a series of dibenzofurans from 2-arylphenols using copper catalysts and additives in hot DMSO (Scheme 3).¹⁷



Scheme 3. Synthesis of dibenzofurans **10** from the cyclization of 2-arylphenols **9** using CuBr and air.

At the beginning of this study, the authors failed to cyclize 2-phenylphenol, used as a model substrate, with various copper salts under an air atmosphere. To overcome this difficulty, 4-nitro-2-phenylphenol **9a**, less subjected to oxidation, was reacted in hot DMSO at 140 °C with one equivalent of PivOH and various copper catalysts and different bases. The best combination of reagents required to use CuBr (30 mol%), PivOH (1 eq) and Cs₂CO₃ (0.5 eq) to transform 4-nitro-2-phenylphenol **9a** into 2-nitrodibenzo[*b,d*]furan **10a** with a good yield of 72%. The scope of this reaction revealed that substituents on both aromatic rings were well tolerated (Me, OMe, Ph, halogens) and that –CN, –CHO and –NO₂ substituents on the *para*-position of phenols **9** were necessary to produce 2-substituted dibenzofurans **10** in moderate to good yields.

To reduce the high reaction temperature from 140 °C to 100 °C,¹⁸ Zhu proposed the same year to use as a directing group, a pre-located amide¹⁹ group (R¹ = NHCOMe, Scheme 4) on the *meta*-position of the phenyl ring to facilitate the copper coordination and the C–H bond cleavage in a concerted-metalation-deprotonation (CMD) process.²⁰

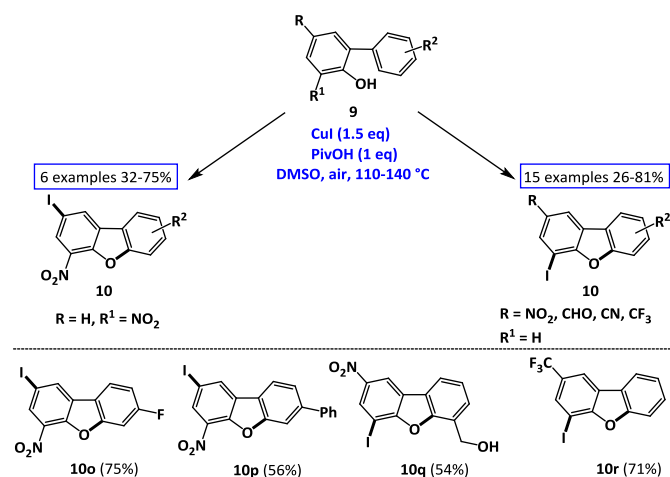


Scheme 4. Synthesis of dibenzofurans **10** from the cyclization of 2-arylphenols **9** using Cu(OAc)₂ and O₂.

The first trial of this study realized with **9k** in the presence of Cu(OAc)₂ (20 mol%), and PivOH (1 eq) was successful, as dibenzofuran **10k** was obtained in a quantitative yield. Zhu observed that the cyclization occurred regioselectively at the *ortho*-position (*o*) close to the acetamide function of phenols **9**, suggesting the existence of chelation of the copper catalyst with both the OH and NHAc functions. The authors showed that NHBoc (**10n**), NHPH or *N*-pyrrolidone can replace the NHCOMe-substituent as a directing group. Zhu proposed a plausible mechanism, depicted

in Scheme 4, which starts with an initial coordination of Cu(II) with the oxygen atom of the phenol and the CO of the amide group to give an intermediate *I*. The Cu(II) activates the *ortho*-C–H bond to provide a plausible oxa-copper cycle *II*. After reductive elimination, dibenzofuran **10** is formed together with a Cu(0) species re-oxidized by O₂ in the presence of pivalic acid.

Zhu and co-workers also reported that CuI in slight excess (1.5 eq) is efficient in these cycloetherification reactions (Scheme 5) to give 2-iodo- or 4-iodo-dibenzofuran derivatives **10** in good yields.²¹



Scheme 5. Synthesis of iodo-dibenzofurans **10** from the cyclization of 2-arylphenols **9** using CuI and air.

In this work, Zhu showed that the process started with an iodination reaction achieved at 110 °C followed by the cycloetherification realized at 140 °C. At the beginning of the process, CuI and O₂ give a Cu(II) species, which oxidizes iodides (I⁻) into molecular iodine (I₂). Then, an iodination reaction generated by I₂ on the *ortho*-position of the phenol (or on *para*-position if a NO₂-substituent occupies the *ortho*-position) occurred. After the cycloetherification reaction, iodinated dibenzofurans were formed, as described above.

2.2 Cycloetherification of phenol derivatives with internal leaving groups (Figure 4).

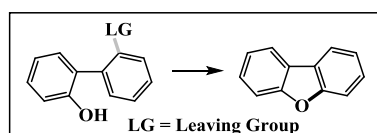
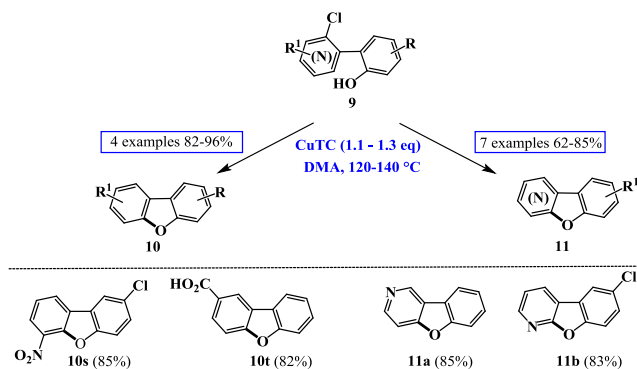


Figure 4.

2.2.1 Cycloetherification of phenol derivatives with nucleophilic displacement of halogens.

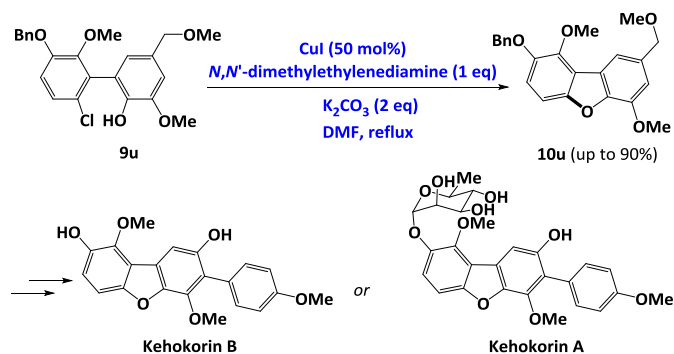
In 2007, Nozaki reported the synthesis of dibenzofurans *via* Pd-catalyzed cycloetherification from the internal coupling of phenols and chlorides or nonaphlates as leaving groups. The best combination of reagents used catalytic amounts of Pd(OAc)₂, 2-di-*tert*-butylphosphino-2'-methylbiphenyl as a ligand, and K₃PO₄ or tBuONa as bases.²² One year after, with the development of methods using copper catalysis, Liu reported the synthesis of dibenzofurans **10** and their nitrogen-containing analogues **11** by cyclizing 2-arylphenols **9** (Scheme 6).²³



Scheme 6. Synthesis of dibenzofurans **10** from the cyclization of 2-arylphenols **9** using CuTC.

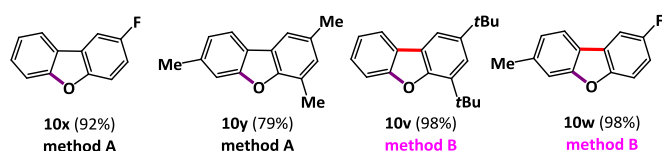
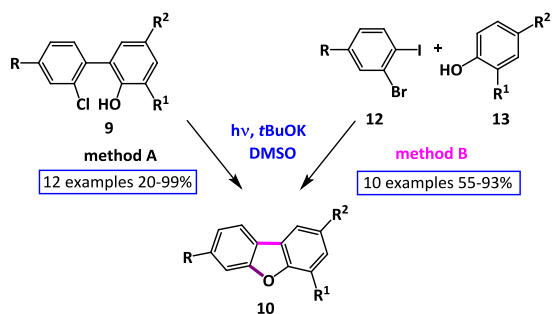
The cyclization of phenols **9** was studied with a large variety of reagents (K₂CO₃, *i*Pr₂NEt, HCl, BF₃-Et₂O, Pd(OAc)₂, CuCl₂, CuCl, and copper(I)thiophene-2-carboxylate (CuTC)). After this investigation, Liu found that CuTC was the most active catalyst for achieving this transformation. The reaction was efficient in DMA or NMP but required a slight excess of CuTC (1.5 eq). This process worked well to construct nitrogen-containing dibenzofurans **11** obtained with good yields. The presence of halogens such as Cl (**11b**), usable for coupling reactions, is well tolerated. This method's main advantage is the relatively mild and neutral conditions since a base is not required.

During the total synthesis of kekorins A and B, cytotoxic dibenzofurans isolated from the myxomycete *Trichia favoginea* var. *persimilis*,²⁴ Fujiwara constructed the dibenzofuran skeleton **10u**²⁵ using the Ullmann coupling reaction realized with CuI, *N,N'*-dimethylethylenediamine, K₂CO₃ in refluxing DMF (Scheme 7).



Scheme 7. Cycloetherification of **9u** leads to dibenzofuran **10u**, a Kehokorin A and B precursor.

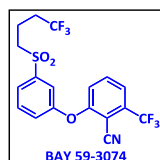
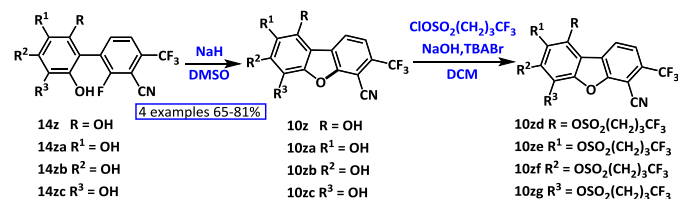
Jimenez generated the C–O bond of dibenzofuran **10** (Scheme 8) using a radical pathway involving photo-induced intramolecular cyclization.²⁶ This work described two strategies implicating electron transfer (eT) reactions for synthesizing variously substituted dibenzofurans **10**. The first one (method A) created the C–O bond of dibenzofurans according to a radical nucleophilic substitution (S_{RN}1) mechanism.²⁶ The second pathway (method B) to dibenzofurans **10** using 1-bromo-2-iodo-aromatic compounds **12** and phenols **13** enables successive creation of the C–C and C–O bonds of dibenzofurans in a one-pot manner. This photo-induced intermolecular reaction is very efficient to give dibenzofurans **10** tolerating substituents of different natures.



Scheme 8. Photo-induced synthesis of dibenzofurans by intra- and inter-molecular pathways.

The authors showed that these reactions were partially inhibited by the addition in the media of *meta*-dinitrobenzene, a strong electron acceptor reinforcing the possible presence of radical anions species. In 2021, Hua reported a similar intermolecular approach²⁷ from phenols and 1-bromo-2-iodobenzenes which were coupled and cyclized in a one-pot manner in DMSO using Cs_2CO_3 (7 examples; 36-70%).

To prepare conformationally constrained analogues of **BAY 59-3074**, a diarylether having a selective binding affinity for cannabinoid receptors, Makriyannis employed the $\text{S}_{\text{N}}\text{Ar}$ reaction for displacing the fluorine atom of phenols **14** (Scheme 9).²⁸



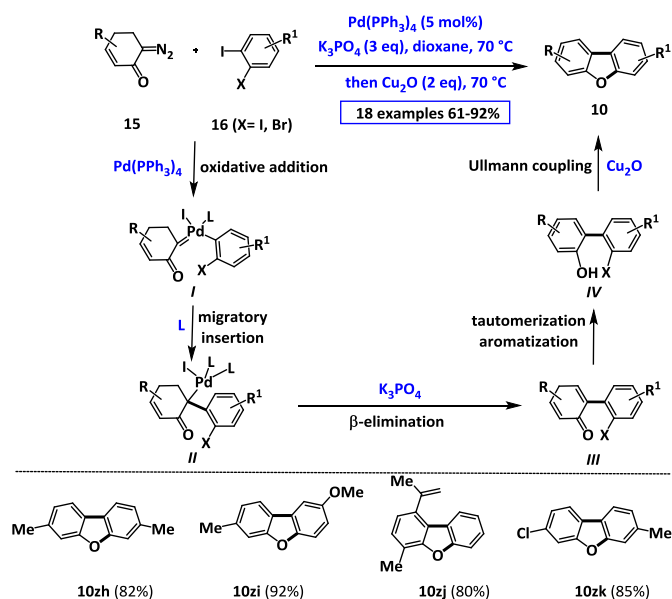
	rCB1 k _i (nM)	mCB2 k _i (nM)	hCB2 k _i (nM)
10zd	55.4	-	45.5
10ze	1900	676	1805
10zf	2526	1709	3290
10zg	1062	339	317
BAY 59-3074	2278	410	253

Scheme 9. Synthesis of dibenzofurans **10** by $\text{S}_{\text{N}}\text{Ar}$ and biological evaluation of **10zd-zg**.

Phenols **14** were subjected to intramolecular cyclization by treatment with NaH in anhydrous DMSO at rt to give the expected dibenzofurans **10z-zc** in good yields (65-81%). A final sulfonylation, achieved with 4,4,4-trifluorobutane-1-sulfonyl chloride, NaOH, and tetrabutylammonium bromide, gave dibenzofurans **10zd-zg** in good yields. However, these constrained analogues had significantly reduced affinities for CB1 and CB2 cannabinoid receptors compared to **BAY-3074**. This result suggests that a planar conformation of ligands is not favourable for optimized anchoring on this receptor type. The $\text{S}_{\text{N}}\text{Ar}$ strategy with the displacement of a fluorine atom under alkaline conditions (K_2CO_3 , NMP) was used a few years later by Nakano and Truong for constructing a series of poly-aromatic dibenzofurans having promising semiconducting properties.²⁹

In 2015, Zhai proposed a one-pot synthesis of dibenzofurans **10** obtained from the reaction between diazo-2-cyclohexenones **15**

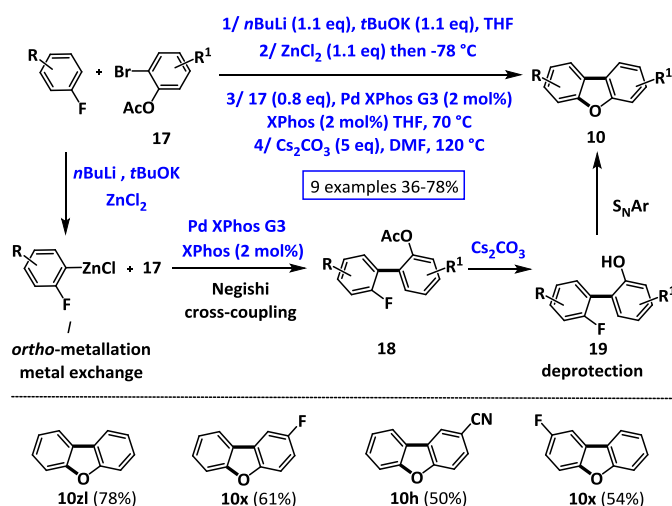
and *ortho*-halo-iodobenzenes **16** with the creation successively of a C-C and a C-O bond (Scheme 10).³⁰



Scheme 10. One-pot Pd-catalyzed cross-coupling followed by Cu-catalyzed Ullmann coupling.

This reaction works well with *ortho*-di-iodobenzenes and *ortho*-bromo-iodobenzene derivatives. The process is also compatible with bulky groups as OTBS substituents, with an additional halogen as a chlorine atom (**10zk**) and, with fragile groups as acetals. The only limitation mentioned in this work concerns electron-poor aromatic nuclei-bearing esters, *p*-CF₃ and *p*-NO₂ substituents, for which the reaction did not work.

In 2023, Roesner and Clarkson reported one-pot access to dibenzofuran from aryl fluorides and *ortho*-bromophenyl acetates **17** by a metalation/Negishi cross-coupling reaction followed by an $\text{S}_{\text{N}}\text{Ar}$ reaction (Scheme 11).³¹

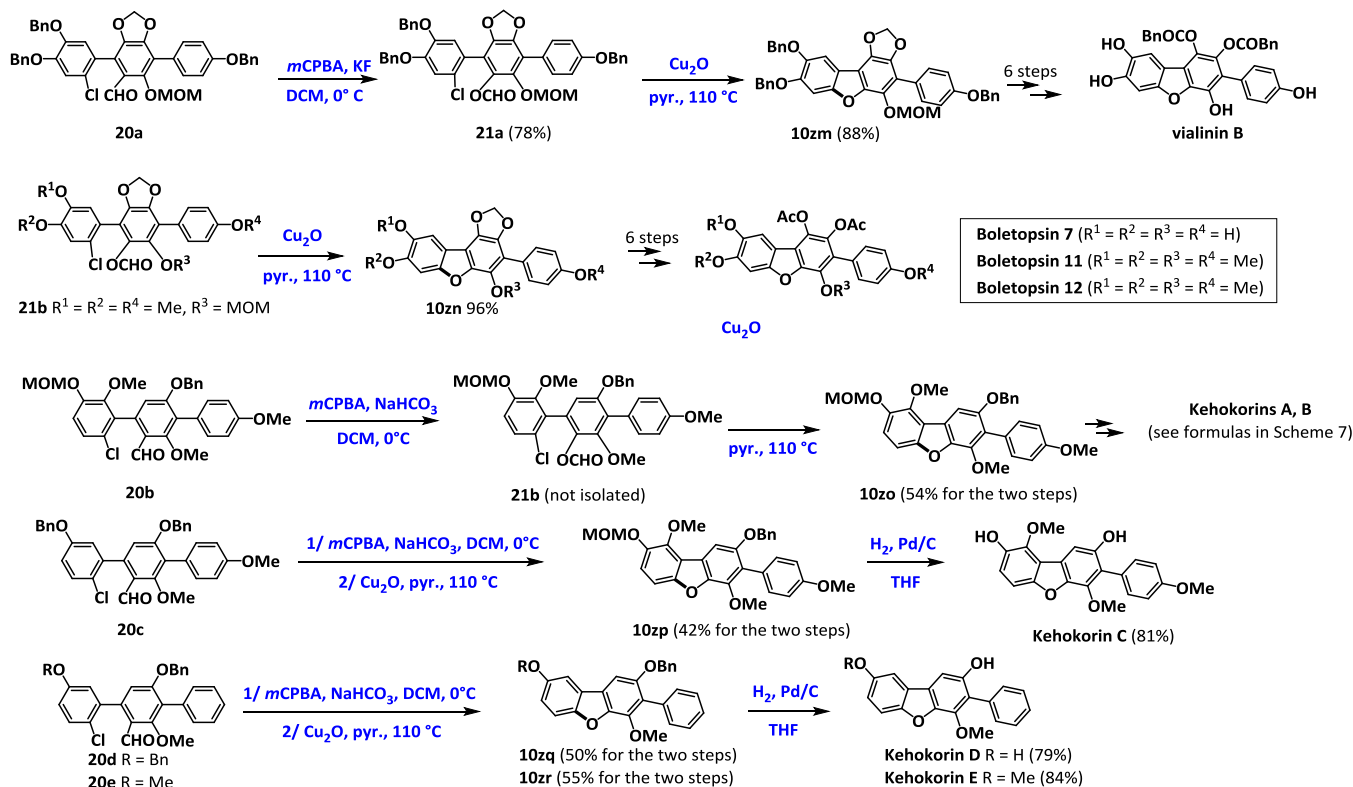


Scheme 11. One-pot synthesis of dibenzofurans **10** from aryl fluorides and *ortho*-bromophenyl acetates **17**.

The authors used the super-basic system $n\text{BuLi}/t\text{BuOK}$ ³² for the *ortho*-metalation of aryl fluorides. Zincation with ZnCl_2 provided the organozinc species **I**, which coupled with *ortho*-bromophenyl acetates **18** in the presence of PdXPhos G3 (2 mol%) and XPhos (2

mol%) in THF to give acetate **18**. After solvent exchange, alkaline deprotection (Cs_2CO_3) of acetate **18** furnishes phenol **19**. This compound then cyclizes by creating the C–O bond of dibenzofuran **10**. It should be interesting to evaluate this process with *meta*-substituted aryl fluorides to possibly prepare dibenzofurans with selectivity by controlling the *ortho*-metalation.

One of the main problems encountered in intramolecular etherification reactions concerns the frequent instability of phenol derivatives. This problem was solved by reacting an acetate as a masked phenol precursor in the presence of *t*BuOK in hot DMSO since a deacetylation reaction precedes cyclization.³³



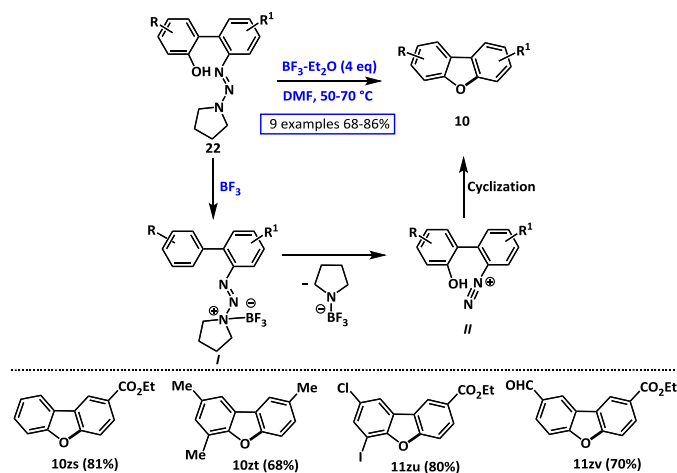
Scheme 12. Synthesis of dibenzofurans from the cyclization of formate derivatives.

2.2.2 Cycloetherification of formates derivatives with nucleophilic displacement of halogens.

For phenols instability reasons, Takahashi oxidized aldehydes **20a** into formate **21a** (78%) (Scheme 12). Cycloetherification of **21a** was achieved using Cu_2O to give dibenzofuran **10zm** with an excellent yield of 88%. Further transformations of **10zm** (6 steps) led to vianilin B, a highly potent inhibitory activity against tumour-necrosis factor (TNF- α). Using this methodology, Barrow proposed five years later the total synthesis of Boletopsins 7, 11, and 12³⁴, which are dibenzofurans isolated from the Papua New Guinean medicinal mushroom *Boletopsis* sp. having 5-lipoxygenase inhibitory activity³⁵ and gastrointestinal properties. Similarly, Takahashi reported in 2017 the total synthesis of Kehokorins A–E³⁶ as cytotoxic dibenzofurans from aldehydes **20b** and **20c–e**, initially oxidized with *m*CPBA in the presence of NaHCO_3 . The resulting formates **21**, used without purification, were heated with Cu_2O to provide the expected dibenzofurans **10zo–zr** with acceptable yields. (42 to 55% for the two steps).

2.2.3 Cycloetherification of phenol derivatives with the displacement of N_2 .

Ren and co-authors developed a Lewis acid-promoted nucleophilic aromatic substitution access to dibenzofurans by reacting phenol-triazene substrates **22** with $\text{BF}_3\text{-Et}_2\text{O}$ in DMF (Scheme 13).³⁷

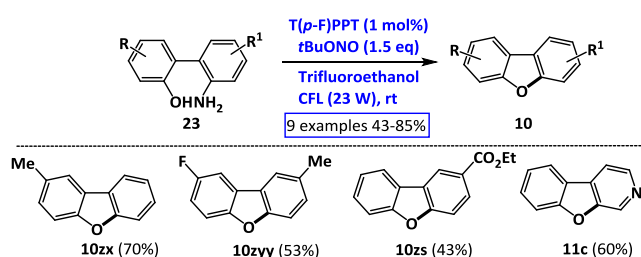


Scheme 13. Cyclization of phenol-triazenes **22** with $\text{BF}_3\text{-Et}_2\text{O}$.

As a possible mechanism, we suggest that $\text{BF}_3\text{-Et}_2\text{O}$ could activate the N–N bond of triazenes **22** through coordination with a nitrogen atom to form intermediates of type *I*. Then, the cleavage of the N–N bond of *I* occurs to furnish diazonium salt³⁸ intermediates *II* which cyclize successfully in dibenzofurans in good yields with reasonable times (3–7 h). Substrates bearing electron-donating and electron-withdrawing groups on the phenols were well tolerated. Moreover, this process is efficient, with phenol-triazenes delivering a variety of possibly transformable substituents such as aldehydes, halogens, or

cyanides. This process applied to aniline-triazenes gave the corresponding carbazoles in high yields.

In the same vein, Cho proposed the formation of the C–O bond of dibenzofurans **10** through the Pschorr cyclization of diazonium intermediates³⁹ (Scheme 14) formed from 2-(2'-aminoaryl)phenols **23** and *tert*-butylnitrite (*t*BuONO).⁴⁰ The authors initially tried to achieve the cyclization of tetrafluoroborate diazonium salts generated from 2-(2'-aminoaryl)phenols **23** and *tert*-butyl nitrite (*t*BuONO) in trifluoroethanol (TFE) at different temperatures. Unfortunately, dibenzofuran yields were low (from 0% at rt to 44% at 60°C). To improve the efficiency of this process, they next investigated the influence of different photosensitizers using a compact fluorescent lamp (CFL, 23 W). After extensive screening (photosensitizers, solvents, stoichiometry of reagents, concentration), the best conditions required the use of 2,4,6-tris(*p*-fluorophenyl)pyrylium tetrafluoroborate (T(*p*-F)PPT) as the sensitizer, TFE as the solvent, and 1.5 eq of *t*BuONO.

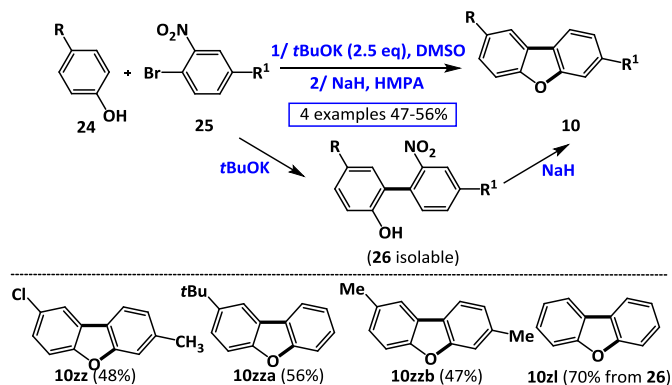


Scheme 14. Visible light promoted synthesis of dibenzofurans **10**.

The reaction is general and compatible with various substituents of different natures on the two aromatic rings. Heteroaromatic rings also worked well for cyclization (**11c**). Moreover, this process was efficient at a gram-scale (0.5 mmol) with no loss of efficiency. Through a single example, Liu also showed that the replacement of the hydroxy by a methoxy substituent did not prevent the cyclization of the corresponding diazonium salt, producing a dibenzofuran after a demethylation step.⁴¹

2.2.4 Cycloetherification of phenol derivatives with the displacement of NO₂.

In 2014, Kumar proposed one-pot access to dibenzofurans **10** by mixing phenol derivatives **24** with *ortho*-bromonitrobenzenes **25** (Scheme 15).⁴² In this work, the authors initially optimized the conditions for preparing various nitrobiarylols **26** from phenols **24** and *ortho*-nitrobenzenes **25**. Without isolating nitrobiarylols **26**, they created the C–O bond of dibenzofurans **10** by alkaline substitution of the NO₂ group.⁴³



Scheme 15. One-pot synthesis of dibenzofurans from phenols **24** and *ortho*-bromonitroarenes **25**.

2.3 Cyclization of *o,o'*-disubstituted biaryl derivatives (Figure 5).

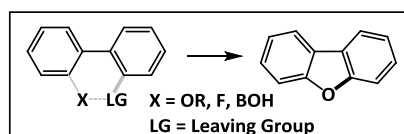
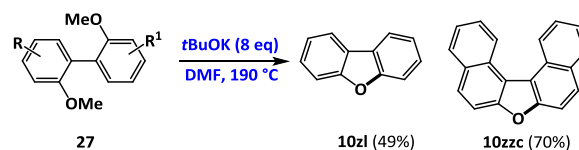


Figure 5.

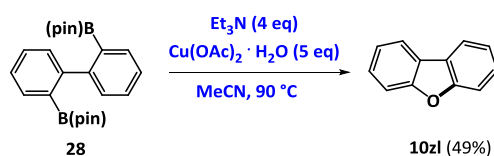
In a study dedicated to the synthesis of dibenzothiophenes through the cleavage of two C–S bonds, Tobisu and Chatani reported the synthesis of dibenzofurans **10zl** and **10zcc** from diarylanisoles **27** (Scheme 16).⁴⁴



Scheme 16. *t*BuOK promoted the synthesis of dibenzofurans **10zl** and **10zcc** in hot DMF.

The authors proposed a possible mechanism based on DFT calculations. First, *t*BuOK reacts on one of the two methoxy-substituents to give, after cleavage of the O–Me bond, a phenolate intermediate and *t*BuOMe. Then, an S_NAr reaction between the phenolate and the second methoxy occurs *via* a Meisenheimer complex to give the expected dibenzofurans after the departure of a methylate anion. However, this process requiring an excess of a strong base in hot DMF (190 °C) is undoubtedly limited to robust anisole substrates.

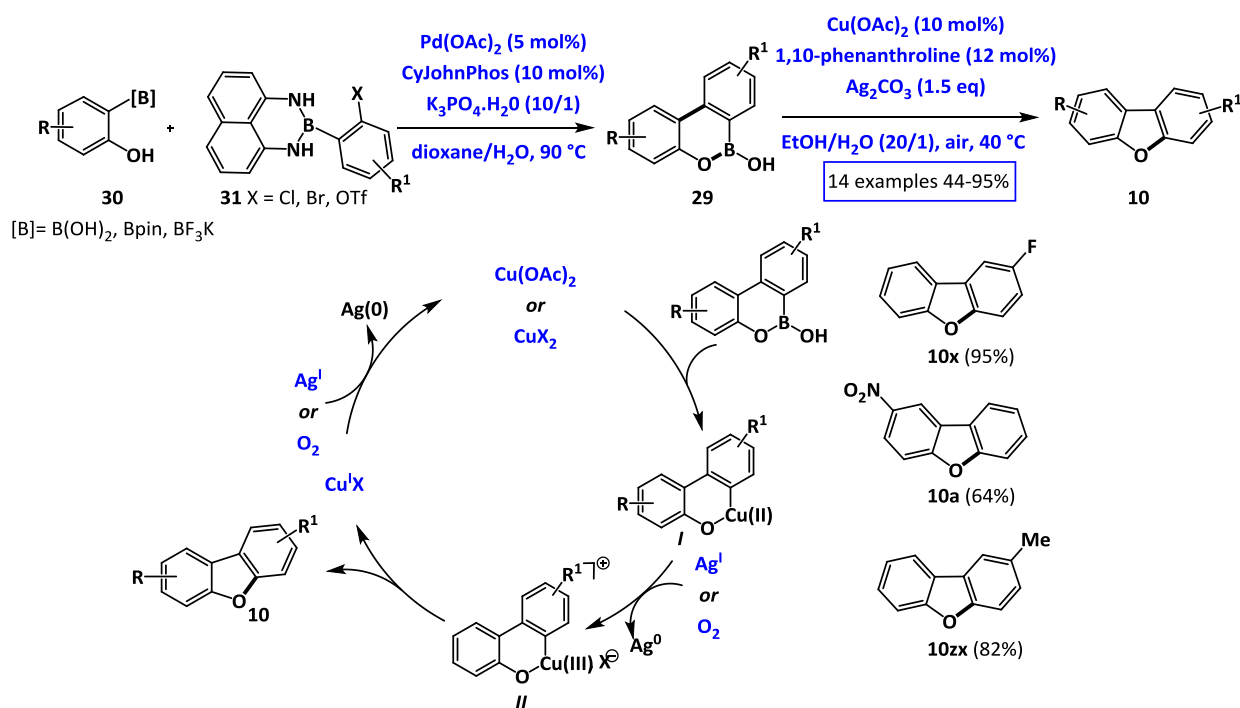
Yorimitsu reported, through a single example (Scheme 17, 49%), the synthesis of dibenzofuran **10zl** (49%) from the cyclization of 2,2'-diborylaryl **28** in the presence of Cu(OAc)₂ and Et₃N.⁴⁵



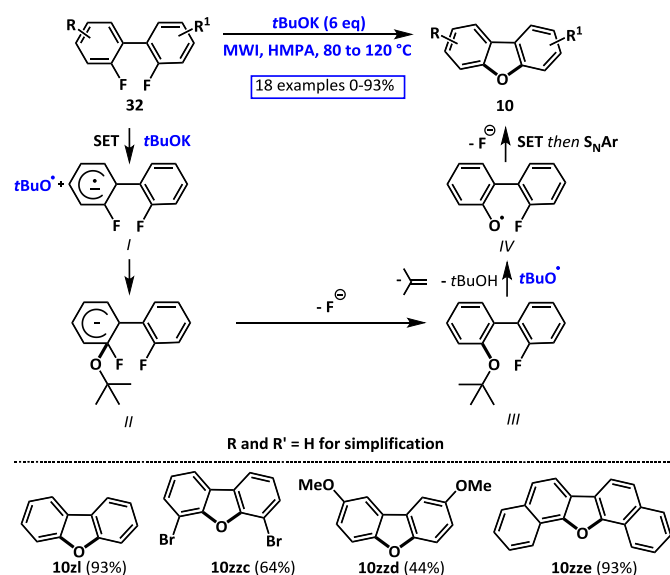
Scheme 17. Cyclization of 2,2'-diborylaryl **28** under Cu-catalysis.

In 2020, Hosoya reported the synthesis of dibenzofurans by Cu-catalyzed deborylative ring contraction of dibenzoxaborin derivatives **29** (Scheme 18).⁴⁶ These compounds were first constructed according to a boron-selective Suzuki cross-coupling reaction between *ortho*-boryl phenols **30** and aryl halides or aryl triflates **31** having on *ortho*'-position a 1,8-diaminonaphthalene-boryl group (Bdan).⁴⁷ The screening of reaction conditions for the final deborylation step followed by ring-contraction of **29** revealed that 1,10-phenanthroline was an efficient ligand of Cu(OAc)₂ and Ag₂CO₃

was the best oxidative reagent for this reaction achieved at 40 °C in wet EtOH. The reaction tolerated electronic groups of different natures at different positions, giving the expected dibenzofurans with good yields. The proposed mechanism starts with the deborylative transmetalation of **29** with Cu(OAc)₂, giving an oxocopa cycle intermediate *I*. Oxidation of *I* by air or Ag₂CO₃ provides a species of type *II*. A final reductive elimination furnishes dibenzofuran **10** together with a copper(I) species which is next re-oxidized by air or Ag₂CO₃, thus continuing the catalytic cycle.



Scheme 18. Deborylative ring contraction of dibenzoxaborins **29**.



Scheme 19. Nucleophilic substitution of 2,2'-difluoro-1,1'-biphenyl compounds **32** by *t*BuOK in HMPA.

Feofanov and Amsharov reported in 2021 the formation of dibenzofurans and π -extended analogues by displacing two fluorine

atoms of 2,2'-difluoro-1,1'-biphenyl compounds **32** by *t*BuOK (Scheme 19).⁴⁸ In this reaction, the oxygen atom of *t*BuOK plays the role of a *bis*-nucleophile. At the beginning of the process, the authors proposed an uncertain mechanism. First, *t*BuOK gives an electron to the aromatic system to form a *t*BuO[•] radical and a radical-anion of type *I*. Then, the *t*BuO[•] radical adds on *I* to give *II* and *III* after the departure of a fluoride anion. A *t*BuO[•] radical then deprotonates the *t*Bu moiety of intermediate *III* to provide a carbon-containing radical, eliminating 2-methylprop-1-ene to give a phenoxy radical *IV*. The reduction of this radical leads to a phenolate intermediate, which finally cyclizes by eliminating a fluoride anion to give dibenzofuran **10**. According to a radical mechanism, the reaction worked well with electron-poor aromatic rings. The method was incompatible with C–I bonds and worked partially with C–Br bonds. This metal-free process gave access to the one-step construction of heterocyclic systems containing two or three dibenzofuran units possibly used in OLED materials. As an alternative, the same team proposed to achieve this oxodefluorination reaction by heating at 190 °C, 2,2'-difluoro-1,1'-biphenyl compounds **32** with activated γ -Al₂O₃.⁴⁹ Using these conditions, iodides on aromatic rings were tolerated.

This first part of the review concerning the synthesis of dibenzofurans by creating the C–O bond shows that there are now many accesses to this heterocycle, either by cyclizing 2-arylphenols

via reactions using the C–H activation or by cyclizing phenols having on *ortho*-position phenyl rings substituted with different leaving groups.

3. SYNTHESIS OF DIBENZOFURANS BY CREATING THE C–C BOND OF THE FURAN RING.

3.1 Synthesis of dibenzofurans by intramolecular dehydrogenative coupling of biaryl derivatives (Figure 6)

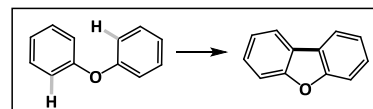
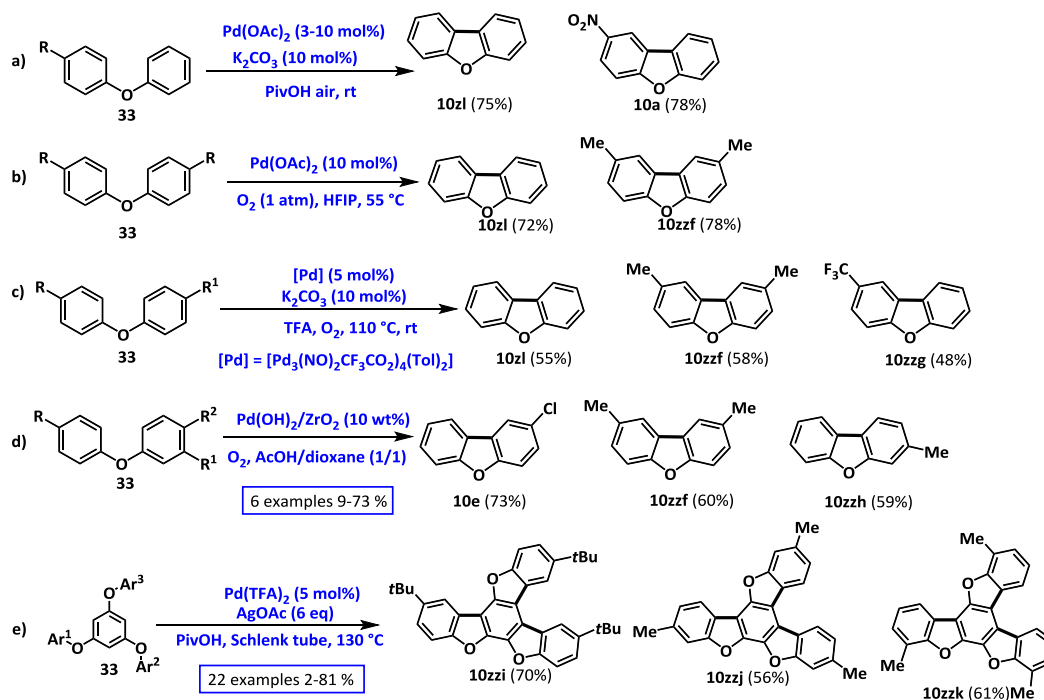


Figure 6.

Following the pioneering work of Shiotani concerning the synthesis of dibenzofurans *via* intramolecular coupling of biaryl ethers under Pd(OAc)₂ catalysis,⁵ numerous modifications/improvements have been proposed since 2008 (Scheme 20).

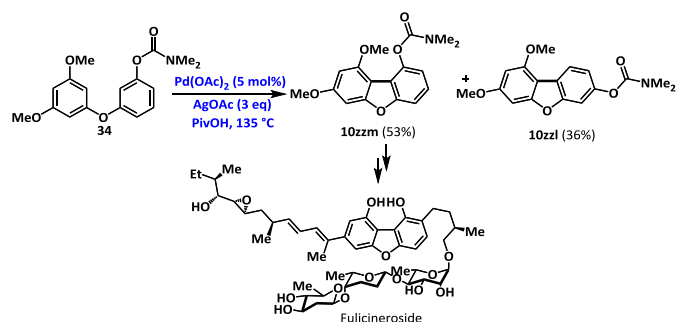


Scheme 20. Pd-catalyzed intramolecular dehydrogenative cyclization of biaryl ethers **32** and **33**.

It appears that palladium catalysis is still the preferred method for this intramolecular cyclization. In 2008, Fagnou proposed a mild intramolecular oxidative process to cyclize biaryl ethers **33** under Pd-catalysis under an air atmosphere at room temperature (Scheme 20a).⁵⁰ The reaction was initiated by palladation of **33** generating a four-membered palladacycle intermediate with the oxygen atom as an *ortho*-directing group. Further C–H cleavage took place *via* two successive CMD processes. A subsequent reductive elimination produced dibenzofuran **10** and generated a Pd(0) species which was oxidized by air. Electronic substituents of different natures are well tolerated, giving dibenzofurans in high yields. Diarylamines were converted into expected carbazoles using this methodology. Wang also used Pd(OAc)₂ to prepare dibenzofurans **10zl** and **10zfz** (Scheme 20b) in HFIP under an oxygen atmosphere in a base-free protocol.⁵¹ Recently, Shishilov showed that palladium nitrosyl complexes were efficient catalysts for C–H/C–H oxidative coupling of arenes of different natures.⁵² This process achieved in hot TFA under an O₂ atmosphere used a Pd₃(NO)₂(CF₃CO₂)₄(tol)₂ complex (5 mol%) which activated arenes to give homocoupling products. The process led to synthesizing various heterocycles as carbazoles, dibenzothiophenes and dibenzofurans (Scheme 20c). Electron-donor and electron-withdrawing groups in the aromatic rings gave similar yields (compare **10zfz** and **10zgz**), and no intermolecular couplings occurred in this silver salts-free protocol. In 2014, Ishida examined several kinds of supported Pd(OH)₂ catalysts

(Pd(OH)₂/Al₂O₃, Pd(OH)₂/TiO₂, Pd(OH)₂/CeO₂ and found that Pd(OH)₂/ZrO₂ (10 wt%) exhibited the highest catalytic activity for synthesizing dibenzofurans in AcOH/dioxane at 130–140 °C under an O₂ (0.25 MPa) (Scheme 20d).⁵³ Yields are good to excellent for this dehydrogenative cyclization, which accepted electron-donating and electron-withdrawing groups on the two aromatic rings. This supported catalyst can be recycled three times and efficiently synthesizes carbazoles from diarylamines. Miura examined in 2016 the catalytic activity of Pd(TFA)₂ in the triple cyclization reaction of ether **33** (Scheme 20e).⁵⁴ Yields in tri-cyclized products were excellent except for substrates having on *para*-position methoxy- or benzoyl-substituents. The cyclization was also applied successfully to 1,2-, 1,3-, and 1,4-diphenoxybenzenes. A substantial UV photoluminescence peak was observed for trioxatruxene **10zkk** ($\lambda_{\text{emis}} = 348 \text{ nm}$ ($\phi = 0.20$)).

However, while these dehydrogenative coupling reactions are effective on simple *ortho*- and *para*-substituted substrates, a lack of selectivity is observed for *meta*-substituted ethers. During the total synthesis of (+)-Fulcineroside, a dibenzofuran with moderate bactericidal activity, Koert obtained a mixture of separable dibenzofurans **10zll** and **10zlm** after cyclization of diarylether **34** (Scheme 21).⁵⁵



Scheme 21. Pd-catalyzed cyclization of biaryl ether **34** and synthesis of Fulcineroside.

3.2 Cyclization of diarylethers with internal leaving groups (Figure 7).

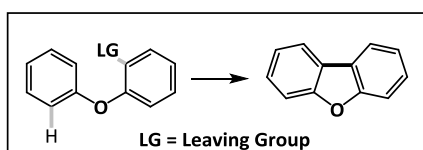
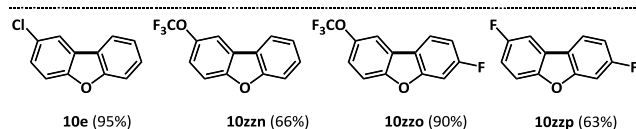
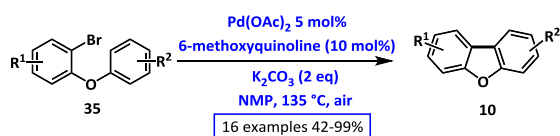


Figure 7.

3.2.1 Cyclization of diarylethers with internal halogens.

Fagnou constructed in 2006 a large variety of heterocycles as 6*H*-benzo[*c*]chromene, carbazoles, and dibenzofurans by Pd(OAc)₂ catalyzed arylation of (benzyloxy)benzenes, diaryl anilines and, diarylethers having an internal halogen atom (Cl, Br, I),⁵⁶ as leaving group. After this work requiring PCy₃·HBF₄ as a Pd-ligand and Ag₂CO₃ (for aryl iodide substrates), McGlacken proposed to associate 6-methoxyquinoline (10 mol%) as a cheap ligand with Pd(OAc)₂ to achieve the cyclization of diarylethers **35** (Scheme 22).⁵⁷

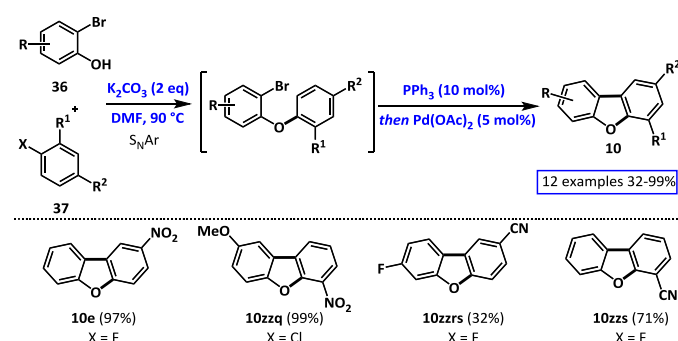


Scheme 22. Pd(OAc)₂ and 6-methoxyquinoline catalyzed arylation of *ortho*-bromo diarylethers **35**.

Among various quinolines evaluated in this study, 6-methoxyquinoline was the more efficient Pd-ligand to accomplish this transformation. Yields were excellent in this phosphine-free ligands process, which tolerated substituents of different natures such as Cl, F, OCF₃, NO₂, CF₃, and others. Under operating conditions described in Scheme 22, diphenylamine reacted to give the corresponding carbazole in moderate yields (50%).

Xu and Fan realized the synthesis of dibenzofurans from aryl halides and *ortho*-bromophenols by first creating a C–O bond by S_NAr followed by an intramolecular cyclization giving access to the dibenzofuran skeleton (Scheme 23).⁵⁸ The S_NAr reaction creating the C–O bond of *ortho*-bromodiarylether intermediates occurred in

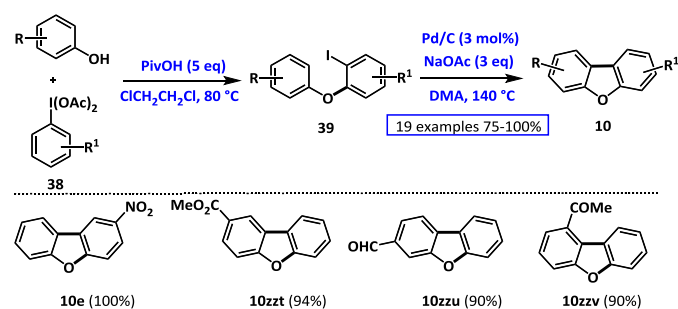
a short reaction time of 0.75 h in hot DMF. Then Pd(OAc)₂ and PPh₃ were added to the crude mixture, and the solution was heated various times depending on the substrates.



Scheme 23. One-pot synthesis of dibenzofurans from *ortho*-bromophenols **36** and electron-poor aryl halides **37**.

Yields for this one-pot process were excellent for aryl halides having in *ortho*- or *para*-position a NO₂ group, whereas results decreased with *ortho*-CN and *para*-CN derivatives **37**. The advantages of this one-pot process are good yields, inexpensive reagents, simplicity, and practical procedure.

In 2015 Panda studied, through 19 examples, the cyclization of a series of *ortho*-iododiarylethers **39** with catalytic amounts of Pd/C (Scheme 24).⁵⁹

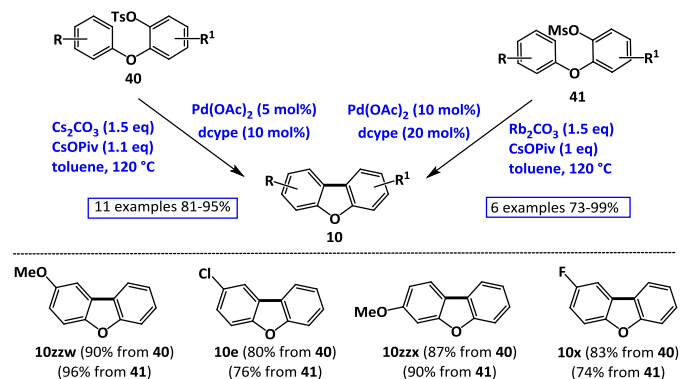


Scheme 24. Pd/C-catalyzed synthesis of dibenzofurans **10**.

The authors initiated their work by finding novel access to *ortho*-halodiarylethers **39**. They mixed electron-poor phenol derivatives with aryl iodide diacetates **38** in different solvents with various additives. Best conditions to obtain *ortho*-halodiarylethers **39** required heating in dichloroethane at 80 °C, phenols derivatives with 1.5 eq of aryl iododiacetates **38** in the presence of 5 eq of pivalic acid (15 examples, 40-98%). Attempts to cyclize *ortho*-halodiarylethers **39** were achieved with different Pd-catalysts as PdCl₂, Pd(PPh₃)₄, Pd/C, Pd(OAc)₂, with various bases as K₂CO₃,⁶⁰ Cs₂CO₃,⁶¹ NaHCO₃, NaOAc in various solvents as DMA, DMF, DCE, THF, and EtOH. Among the different combinations, the authors showed that Pd/C (3 mol%) associated with NaOAc (3 eq) in hot DMA gave the best yields in dibenzofurans. The Pd/C catalyst used for the cyclization reaction was recovered by filtration and may also be used for subsequent coupling reactions. However, if results were excellent for dibenzofurans **10** having electron-withdrawing groups (NO₂, CO₂R, COMe, CN, and CHO), no example of dibenzofurans bearing electron-donor substituents was described in this article.

3.2.2 Cyclization of diarylethers with internal tosylates, mesylates, and pivalates.

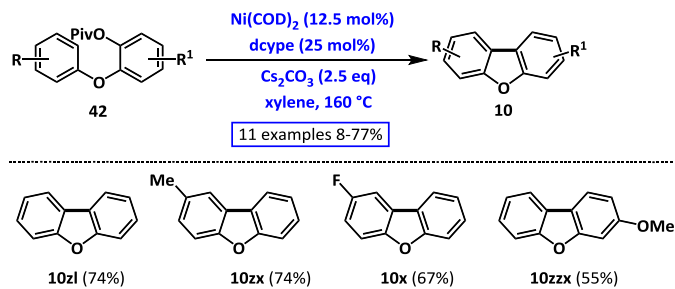
Kalyani studied intensively the Pd-catalyzed intramolecular C–H arylation of arenes **40** and **41** bearing tosylates and mesylates as leaving groups (Scheme 25).⁶² First, the authors started their study by optimizing conditions for the intramolecular cyclization of tosylate substrates **40**. With cesium carbonate as a base and cesium pivalate as an additive, they found that 1,2-*bis*(dicyclohexylphosphino)ethane (dcype) was the best ligand for the palladium catalyst (Pd(OAc)₂). Using these operating conditions, they prepared a series of dibenzofurans **10** having electron-rich and electron-poor substituents on both aromatic rings.



Scheme 25. Pd(OAc)₂ and dcype catalyzed internal arylation of *ortho*-OTs-diarylethers **40** and *ortho*-OMs-diarylethers **41**.

Excellent regioselectivity was observed for challenging *meta*-substituted ethers with two different aromatic C–H bonds which were converted into *meta*-substituted dibenzofuran (**10zzx**). The reaction occurred at the less sterically hindered C–H bond for these substrates. Dibenzofurans were also prepared from the cyclization of mesylate compounds **41**. For the cyclization of such diarylethers, Rb₂CO₃ replaced Cs₂CO₃ and the quantity of catalyst and ligand was doubled. As illustrated in Scheme 25, dibenzofuran yields were comparable using tosylates **40** or mesylates **41**. A one-pot sequential tosylation or mesylation followed by cyclization was successfully applied to free phenols to afford the expected dibenzofurans in high yields. Finally, the authors used these operating conditions to convert various diarylamines into the corresponding carbazoles (82% to 92%).

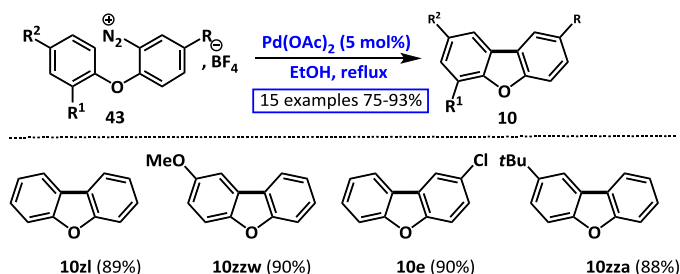
Kalyani showed that Ni-catalysis also efficiently cyclized diarylethers **42**, having internal pivalates as leaving groups (Scheme 26).⁶³ Best conditions to achieve this transformation in hot xylene associated Ni(COD)₂ as the catalyst with dcype as the ligand and Cs₂CO₃ as the base. The reaction tolerated electron-rich and electron-poor substituents on both aromatic rings, giving dibenzofuran **10** with moderate to good yields. The major drawback of the process was the persistent formation of proto-deoxygenated diarylethers resulting from a non-desired C–OPiv bond cleavage (~25%). Kalyani evaluated other leaving groups for comparisons. The results of this study revealed that this concerted-metalation-deprotonation process furnished dibenzofuran **10zl** (74%) in variable yields (LG = OPiv, 74%), (LG = OCONe₂, 40%), (LG = OTs, 4%), (LG = OBz, 22%), (LG = OCO(*p*-OMeC₆H₄), 5%), (LG = OCO(*p*-CF₃C₆H₄), 0%). Notably, this Ni-catalyzed process also worked well with diaryl-*N*-methylanilines, giving the corresponding *N*-methyl carbazoles.



Scheme 26. Ni-catalyzed C–H arylation/cyclization of pivalates **42**.

3.2.3 Cyclization of diarylethers with internal diazonium salts.

Following the pioneering work of Wassmundt and Pedemonte,¹² Gajera synthesized two dibenzofurans through a Cu-catalyzed intramolecular cyclization of 2-phenoxy-benzenediazonium salts.⁶⁴ However, the cyclization conditions required a significant excess of Cu₂O (1.5 eq) in H₂SO₄. As an improvement, Du and co-workers proposed in 2011 to use Pd(OAc)₂ (5 mol%) in refluxing EtOH to displace internal diazonium tetrafluoroborates (Scheme 27).⁶⁵

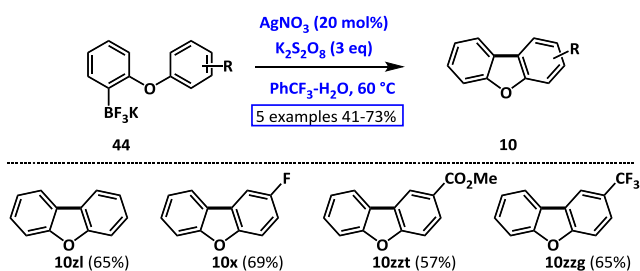


Scheme 27. Pd(OAc)₂-catalyzed cyclization of diarylethers **43**.

The reaction was tolerant with various functional groups (Cl, Br, F, CO₂Et, CO₂Ph, OMe, and *t*Bu) on both aromatic rings. Without any bases, EtOH was superior to DMF, DCM, MeCN, and MeOH to achieve this cyclization reaction and was also used to reduce the Pd(OAc)₂ to a Pd(0) species.⁶⁶ After oxidative addition of the Pd(0) and elimination of N₂, an aryl-Pd species is formed. Subsequent insertion of an aromatic C–H bond to the Pd(II) metal gives a 6-membered oxo-Pd-ring. Reductive elimination of Pd(II) furnishes the Pd(0) catalyst and gives the dibenzofuran after the creation of the C–C bond. The major advantage of this process is its versatility, the absence of bases and the use of EtOH as a green solvent.⁶⁷

3.2.4 Cyclization of diarylethers with internal trifluoroborates.

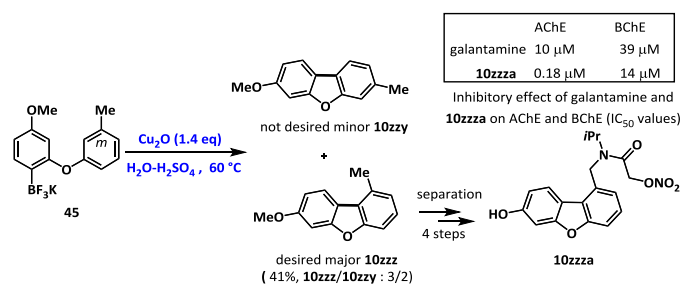
In 2011, Baran demonstrated that internal trifluoroborate substituents were adequate leaving groups for cyclization reaction of diarylethers **44** (Scheme 28).⁶⁸ This borono-Pschorr process tolerated sensitive groups such as esters and nitriles, can be conducted on a gram-scale, and did not involve high temperatures. With a *meta*-substituent (R = *m*-OMe), 1-methoxy-dibenzofuran was mainly



Scheme 28. Synthesis of dibenzofurans **10** by radical cyclization of diarylethers **44**.

obtained together with 3-methoxy-dibenzofuran with a good regioselectivity (5/1). This process has the advantage of being effective in water in an open-air flask and uses only a catalytic amount of AgNO_3 and 3 eq $\text{K}_2\text{S}_2\text{O}_8$. The authors suggest a mechanistic hypothesis where a silver cation mediated decomposition of $\text{S}_2\text{O}_8^{2-}$ anion to give two radical species $\text{SO}_4^{\bullet-}$. This radical then reacts with the trifluoroborate substituent, resulting in selective fragmentation of the weak aryl-boron bond. Then, the aryl radical formed undergoes cyclization with the closer C–H bond of the aromatic ring.

During the synthesis and biological evaluation of dibenzofurans having anti-Alzheimer properties, Fleck observed a similar regioselectivity during the cyclization of *meta*-substituted diarylether **45** using Cu_2O in H_2SO_4 (Scheme 29).⁶⁹ The authors did not comment on the regioselectivity of the cyclization, which slightly exceeded the desired dibenzofuran **10zzz**.

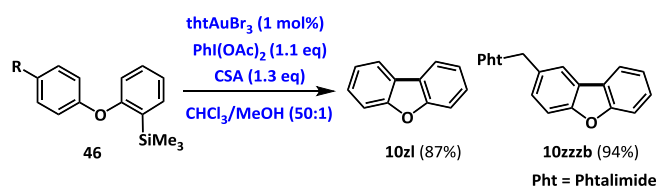


Scheme 29. Cu_2O -catalyzed cyclization of diarylether **45**; access to biologically active dibenzofuran **10zza**.

After separation of the regioisomers and functionalization, the authors prepared, a series of dibenzofurans in which **10zza** was the more promising compound. An evaluation revealed that dibenzofuran **10zza** exhibited potent inhibition activity towards acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). This dibenzofuran showed a promising A β 42 aggregation inhibitory activity, could release a low NO concentration *in vitro*, and was not cytotoxic towards neuronal cells. *In vivo* evaluation revealed that dibenzofuran **10zza** showed a significant spatial memory-improving effect.

3.2.5 Cyclization of diarylethers with internal silanes.

In 2017, Lloyd-Jones studied intensively the intramolecular gold-catalyzed cyclization of various arenes having trimethylsilane as a leaving group. This process described through 44 examples of 5- to 9-membered rings worked well to build dibenzofurans (Scheme 30).⁷⁰

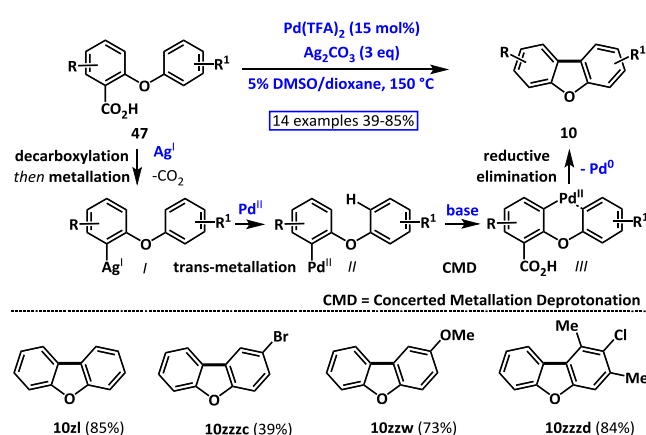


Scheme 30. Gold-catalyzed cyclization of diarylethers **46**.

Best conditions to achieve this cyclization required to use 1 mol % of tthAuBr_3 precatalyst (tth = tetrahydrothiophene), [hydroxy-(((+)-10-camphorsulfonyl)oxy)iodo]benzene (HCIB) which is formed from PhI(OAc)_2 and (+)-10-camphorsulfonic acid (CSA)⁷¹ as the oxidant system, in $\text{CHCl}_3/\text{MeOH}$ (50:1) at rt. The process tolerated various functional groups and worked well with various aromatic rings separated by linkers of different sizes. The authors studied the mechanism of this process, which starts with a transmetalation of the arylsilane moiety with the gold(III)-catalyst. Then, the C–H auration on the second aromatic ring proceeds *via* an aromatic electrophilic substitution ($\text{S}_{\text{E}}\text{Ar}$) to give a 6-membered gold(III) ring intermediate. Final reductive elimination furnishes the dibenzofuran with a gold(I) species which is re-oxidized by HCIB to continue the catalytic cycle.

3.2.6 Cyclization of diarylethers with internal carboxylic acids.

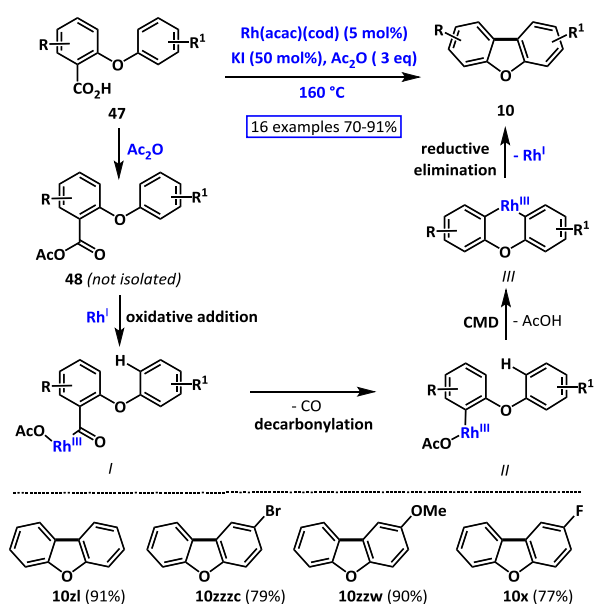
Glorius proposed in 2009 to use a carboxylic acid as a leaving group for synthesizing a variety of dibenzofuran according to a palladium-catalyzed decarboxylation/C–H functionalization sequence of diarylethers **47** (Scheme 31).⁷²



Scheme 31. Pd-catalyzed decarboxylative intramolecular C–H arylation of diarylethers **47**.

After investigation of oxidizing agents and bases (Cu(OAc)_2 , CuCO_3 , K_2CO_3 , Ag_2O , Ag_2CO_3 , AgOAc , and AgOTf) and Pd-catalysts (PdCl_2 , Pd(OAc)_2 , and Pd(TFA)_2), the authors determined that best conditions required to heat diarylethers **47** with a combination of Pd(TFA)_2 (15 mol%) and Ag_2CO_3 (3 eq) at 150 °C in dioxane containing 5% of DMSO. Thus, this process provided various dibenzofurans in yields ranging from 39% to 45%. Electronic groups of different natures were well accepted on aromatic rings (Me, OMe, *t*Bu, F, Cl, Br, vinyl, and naphthyl). As no loss of halogens was observed during the reaction, this process seems more advantageous than that developed by Shen later,⁷³ who prepared dibenzofurans from arene carboxylic acids *via* a Pd-catalyzed decarboxylation followed by intramolecular cyclization with a halogen atom used as leaving group.

To decrease the quantity of the catalyst used for this decarboxylation/C–H activation from 15 mol% to 5 mol%, Ryu proposed to replace Pd(TFA)₂ with Rh(acac)(cod) (Scheme 32).⁷⁴



Scheme 32. Rh-catalyzed decarbonylative intramolecular C–H arylation of diarylethers **47**.

Among the Rh-catalysts tested, Rh(acac)(cod) exhibited the highest catalytic activity to achieve the reaction in the presence of Ac₂O and KI. The authors did not explain the exact role of KI in this reaction. A first condensation of diarylether **47** with Ac₂O furnishes the mixed anhydride **48**, which is not isolated. Oxidative addition of the Rh(I)-catalyst leads to an acylrhodium(III) intermediate *I*, which undergoes decarboxylation to give an arylrhodium intermediate of type *II*. Then, C–H activation occurs, providing a rhodacycle of type *III* which produces the desired dibenzofuran after reductive elimination and the regeneration of the Rh(I)-catalyst. Yields were good to excellent, and various substituents of different natures were well tolerated.

The comparison between the Pd- and Rh-decarbonylative/C–H arylation process presented in Schemes 31 and 32 shows that the Rh-system generally gives better yields. It is important to note that both methods allow the preparation of halogen-containing dibenzofurans that could be useful in subsequent metal-catalyzed coupling processes.

3.3 Cyclization of *ortho-ortho'*-substituted diarylethers (Figure 8).

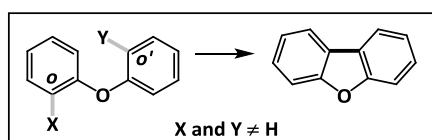
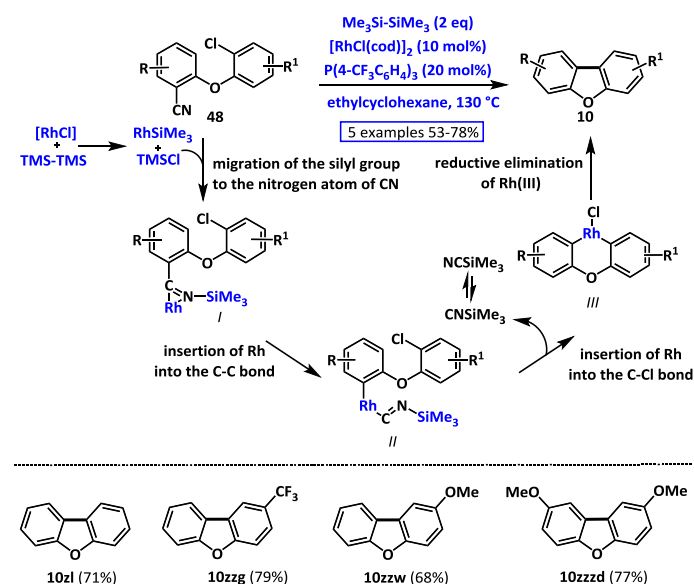


Figure 8.

Chatani and Tobisu found a rhodium-catalyzed silylation of aryl cyanides using hexamethyldisilane.⁷⁵ Applying the best conditions ([RhCl(cod)]₂; (10 mol%), Me₃Si–SiMe₃; (2 eq), P(*p*-CF₃C₆H₄)₃; (20 mol%) in ethylcyclohexane at 130 °C), they transformed *ortho-ortho'*-disubstituted diarylethers **48** into dibenzofurans in good

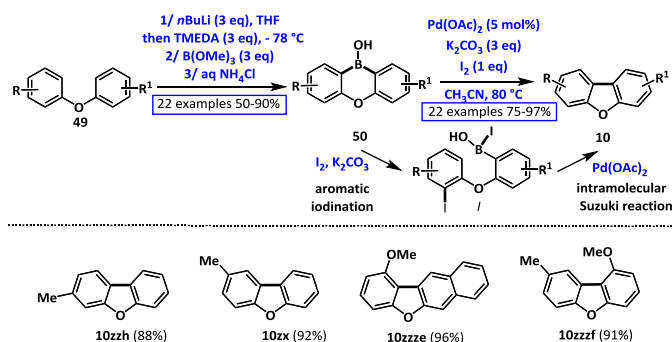
yields (Scheme 33). The authors studied in detail a possible mechanism of the Rh-catalyzed silylation reaction of the carbon–cyano bond using hexamethyldisilane (HMDS). First, reacting the [RhCl(cod)]₂ catalyst with HMDS would afford a Rh(I)SiMe₃ species which adds on the nitrile function to give an η²-iminoacyl complex *I*. Then, the rhodium center migrates into the C–C bond to form an aryl complex intermediate *II*. In the presence of a chlorine atom serving as an internal leaving group, the rhodium center migrates into the C–Cl bond to form a 6-membered rhodacycle of type *III*.



Scheme 33. Rh-catalyzed intramolecular arylation of diarylethers **48**.

Reductive elimination produces dibenzofuran **10** and regenerates the Rh catalyst, completing the catalytic cycle. This reaction furnished dibenzofurans in good yields and tolerated electronic groups of different natures (esters, amides, amines, ethers, boronic esters, CF₃, and heterocycles). The authors showed that a chlorine atom was more reactive as a leaving group when compared to a bromine atom. The process gave access to various tricyclic rings, such as carbazoles and fluorenes. Moreover, this silicon-assisted strategy is of great interest to introduce a rhodium atom into the Ar–CN bond to synthesize a large variety of arylsilanes⁷⁶ and heteroaromatic systems from benzonitriles or phenyl-acetonitrile derivatives. In 2020, Gosmini and Gandon synthesized dibenzofuran **10zl** (77 %) from benzonitrile **48** (R = R' = H) by replacing the Rh-catalyst with a combination of CoBr₂BiPy₂ and Mn(O).⁷⁷

Fu reported an efficient synthesis of a series of dibenzofurans **10** from dibenzoxaborinols **50** readily obtained from the borylation of diarylethers **49** (Scheme 34).⁷⁸ The best borylation conditions of diarylethers **49** required *n*BuLi (3 eq) as the base and TMEDA (3 eq) as an additive in anhydrous THF at –78 °C. In a second step, the resulting *bis*-anion reacted with 3 eq of B(OMe)₃ at rt, and the solution was then quenched with aq NH₄Cl. For *meta*-substituted diarylethers and arylnaphtyl ethers, a good to excellent regioselectivity for the cyclization step was observed. Due to the experimental conditions using *n*BuLi, this process is limited to robust substrates bearing only alkyl- and alkoxy-substituents. The deborylation reaction was achieved with Pd(OAc)₂, K₂CO₃ and I₂, giving dibenzofurans **10** in excellent yields.



Scheme 34. Synthesis of dibenzofurans from dibenzoxaborinols

50.

The authors showed that I₂ was necessary to accomplish this deborylation, indicating that the formation of the C–C bond could not go through a double transmetalation/reductive elimination sequence. After some control experiments, they proposed a mechanism where I₂ and K₂CO₃ react with dibenzoxaborinol **50** to give an aryl iodide intermediate of type *I*. A subsequent Pd-catalyzed intramolecular Suzuki coupling of *I* leads to constructing the C–C bond of the dibenzofuran system. However, the formation of a diaryliodonium intermediate cannot be ruled out.⁷⁹

4. CONSTRUCTION OF DIBENZOFURANS FROM BENZOFURAN OR PHENOL DERIVATIVES (FIGURE 9).

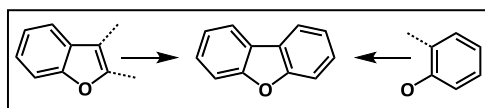
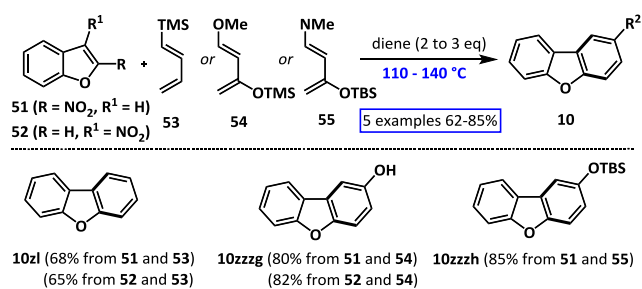


Figure 9.

Before 2008, a few dibenzofurans have been synthesized from benzofuran derivatives. We can mention, for example, the work of Liebesking and Wang, who constructed this nucleus by coupling 2-(*tri-n*butylstannyl)benzofuran to various 4-chloro-cyclobuten-1-ones (5 examples, 65-94%).⁸⁰ Over the last fifteen years, most processes for attaching a benzene ring to a benzofuran have involved Diels-Alder or other cyclization reactions. In addition, the creation of this tricyclic motif from a single benzene ring has also been reported recently *via* cycloaddition, electrocyclization and other annulation reactions.

4.1 Construction of dibenzofurans from benzofurans.

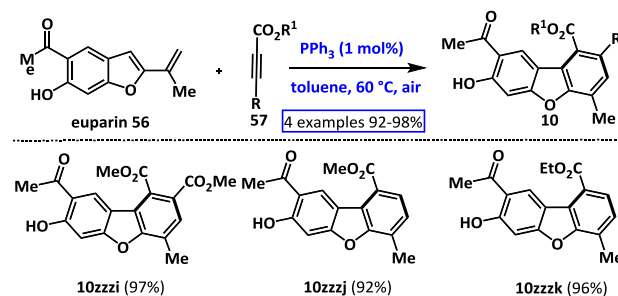
Mancini reported in 2011 a Diels-Alder process to prepare dibenzofurans from 2-nitrobenzofurans and electron-rich dienes (Scheme 35).⁸¹ In this work, Mancini tested 2- and 3-nitrobenzofurans **51** and **52** with a variety of dienes, including 1-trimethylsilyloxy-1,3-butadiene **53**, Danishefsky's diene **54**, and Rawal's diene **55**. Reacting dienes **53-55** with nitrobenzofurans **51** or **52** gave the expected dibenzofurans **10** with good yields and total regioselectivity. The presence of a nitrogroup on benzofurans **51** or **52** enhanced the cycloaddition by favoring the aromatization thus preventing the retrocycloaddition.



Scheme 35. Synthesis of dibenzofurans **10** from Diels-Alder reaction between nitrobenzofurans and dienes.

The authors showed that the OTBS group of Rawal's diene **55** survives under the operating conditions used, unlike the OTMS group of Danishefsky's diene **54**, which was hydrolyzed.

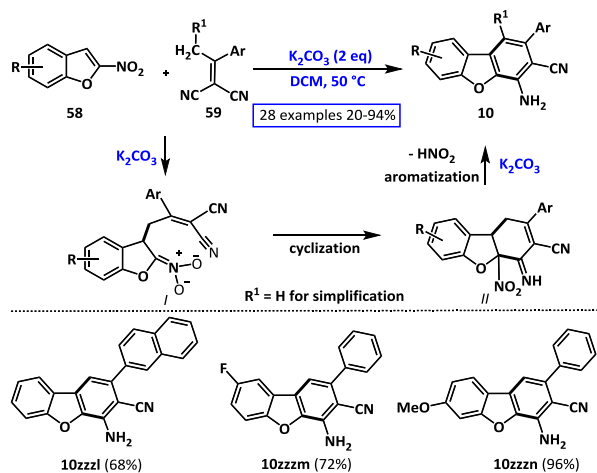
Another Diels-Alder reaction was proposed five years later by Maghsoodlou, who synthesized various dibenzofurans by reacting euparin **56** with acetylenic esters **57** in the presence of PPh₃ (Scheme 36).⁸²



Scheme 36. Synthesis of dibenzofurans **10** from Diels-Alder reaction between euparin **56** and propiolates **57**.

The authors found that toluene was the best solvent to achieve the reaction, which worked only with PPh₃ (1 mol%). Propiolates reacted with euparin with excellent yields and total regioselectivity. Maghsoodlou explained the regioselectivity by a first addition of PPh₃ on the propiolate and the resulting zwitterionic intermediate adds on the C3-position of the benzofuran. This process offers the advantage of excellent yields, complete regioselectivity, and simple purification.

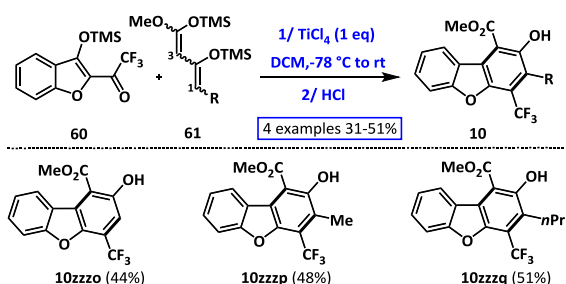
Recently, Yang reported a cyclization reaction for synthesizing dibenzofurans **10** from 2-nitrobenzofurans **58** and alkylidene malonitriles **59** (Scheme 37).⁸³ The reaction achieved at 50 °C in DCM required only K₂CO₃ as a reagent and tolerated electronic substituents of different natures (halogens, alkoxy, alkyl) to give poly-substituted dibenzofurans in moderate to excellent yields. The authors explained this reaction by a first deprotonation of the alkylidene malonitrile **59** by K₂CO₃, giving an anion which adds on the C3 atom of the 2-nitrobenzofuran in a Michael reaction. A cyclization reaction then occurs between the C2 atom of the benzofuran and one of the two nitriles of **59** to give intermediate *II*. Finally, imine-enamine isomerization and loss of HNO₂ (with the help of K₂CO₃) provide dibenzofurans **10**.



Scheme 37. Synthesis of poly-substituted dibenzofurans from 2-nitrobenzofurans and alkylidene malonitriles **59**.

This process furnishes highly functionalized dibenzofurans is enjoyable because it works at a moderate temperature and does not need metal catalysts. Moreover, a NH_2 function is created and can be exploited later for chemical transformations.

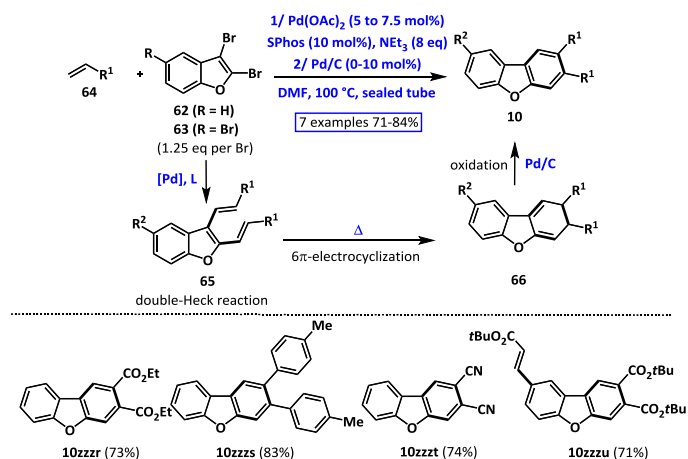
Langer reported in 2012 a TiCl_4 mediated formal [3+3] cyclization of silyl enol ether **60** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **61** (Scheme 38).⁸⁴



Scheme 38. TiCl_4 mediated cyclization of silyl enol ether **60** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **61**.

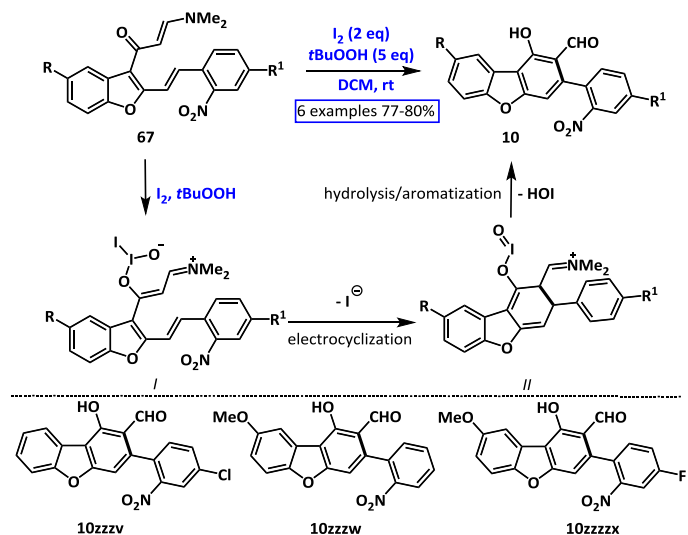
Butadienes **61** reacted with 1 eq of TiCl_4 as related bis-anions⁸⁵ of β -ketoesters and added in a [3+3] process on benzofuran **60** with total regioselectivity. In this reaction, the oxygen atom of the benzofuran nucleus plays a significant role in the regioselectivity of the addition. In the presence of TiCl_4 , the nucleophilic C1 atom of **61** reacts first on the more electrophilic carbonyl group of COCF_3 , and the C3 atom of **61** attacks the carbon attached to the silyloxy group of benzofuran **60**. After acidic hydrolysis and aromatization, tri- and tetra-substituted dibenzofurans are obtained with moderate yields.

In 2009, Langer reported an efficient synthesis of functionalized dibenzofurans **10** by domino Heck reactions followed by 6π -electrocyclization of bromobenzofurans **62** and **63** (Scheme 39).⁸⁶ A double Heck reaction of 2,3-dibromobenzofuran **62** with acrylates **64** ($\text{R}^1 = \text{Et}, n\text{Bu}, i\text{Bu}, \text{tBu}$) produced cyclic intermediates of type **66** readily obtained after electrocyclization of vinyl intermediates **65**. After double bond migration and *in situ* Pd/C oxidation, dibenzofurans **66** were isolated in good yields. When $\text{R}^1 = p\text{-tolyl}$ or CN , Pd/C was not necessary as the expected dibenzofurans were directly obtained (e.g. **10zzzs** and **10zzzt**).



Scheme 39. Heck/ 6π -electrocyclization of various bromobenzofurans **62** and **63**.

The authors demonstrated that the formation of 2,3,5-tribromobenzofuran **63**, started first by a Heck reaction at the C2 then at the C3 atom of **63** and, at least, at position C5. It would, therefore, seem that the order of reactivity of the C3 and C5 bromine atoms in compound **63** differs depending on whether a Heck (C3 > C5) or Kumada reaction is performed C5 > C3.⁸⁷

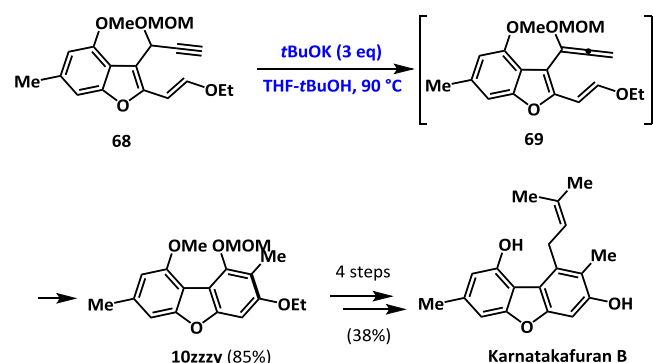


Scheme 40. Electrocylation of benzofurans **67** in the presence of I_2 and TBHP.

During the construction of oxacalothrixin B and analogues with possible anticancer activities, Mohanakrishnan created the dibenzofuran system according to an electrocyclization reaction of enamines **67** in the presence of I_2 and $t\text{BuOOH}$ (Scheme 40).⁸⁸ A series of six enamines **67** were transformed into the respective 2-CHO-benzofuran **10** in good yields at rt in DCM. This electrocyclization reaction was only studied with benzofurans **67** having on C5 no substituent ($\text{R} = \text{H}$) or a methoxy substituent ($\text{R} = \text{OMe}$). The authors showed that halogen atoms ($\text{R}^1 = \text{Cl}$ or F) were well tolerated in this process and could be used later in metal-catalyzed reactions. Mohanakrishnan proposed a mechanism that begins with the formation of a triene intermediate **I** obtained from the coordination of trivalent iodinated species with enamines **67**. After the loss of iodide and electrocyclization, a 2,3-dihydrodibenzo[*b,d*]furan **II** could be formed. Hydrolysis of

intermediate **II** and aromatization furnish dibenzofuran **10** as a precursor of oxacalothrixin B and analogues.

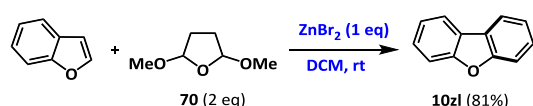
Hieda and Choshi reported in 2023 total synthesis of karnatakafuran B having antimalarial properties using as a key step, the cyclization of benzofuran **68** via an electrocyclization reaction of an allene intermediate **69** (Scheme 41).⁸⁹



Scheme 41. Synthesis of karnatakafuran B from propargyl ether **68**.

Further transformations of the resulting dibenzofuran **10zzzy** gave Karnatakafuran B with a good yield (38%, 4 steps). The authors constructed the dibenzofuran framework using allene-mediated 6π -electrocyclization of propargyl ether **68**. Compound **68** was heated at 90 °C in *t*BuOH in the presence of *t*BuOK, according to the procedure of Kanematsu for allene generation,⁹⁰ to yield the expected dibenzofuran **10zzzy** (85%). After an OTf/OMOM exchange followed by the cleavage of the OMe and OEt ether functions and introducing a prenyl group according to a Suzuki reaction, karnatakafuran B was obtained in an excellent global yield.

To conclude this part dedicated to constructing dibenzofurans from benzofurans, it is interesting to present a Lewis acid-mediated benzannulation of electron-rich arenes.⁹¹ Mohanakrishnan proposed in 2014 an efficient protocol to prepare a variety of cyclic and heterocyclic systems, including dibenzofuran **10zl** involving annulation of various heterocycles with 2,5-dimethoxytetrahydrofuran **70** (Scheme 42).



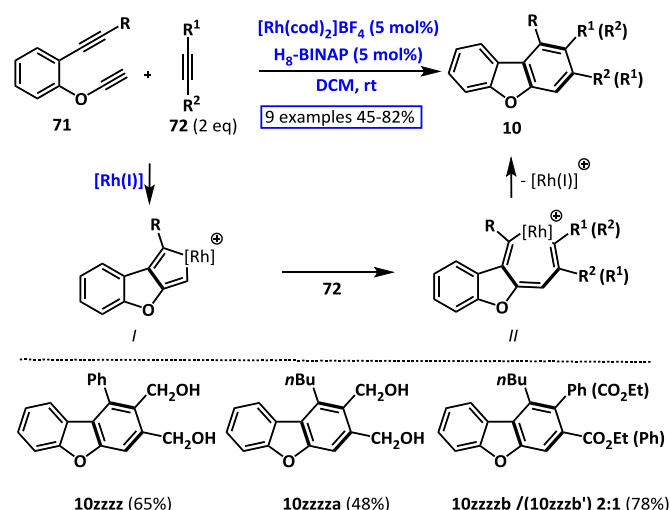
Scheme 42. ZnBr₂-Catalyzed benzannulation of benzofuran with **70**.

The reactions worked well with electron-rich arenes as thiophenes, benzofurans, selenophenes, and pyrroles. This benzannulation is attractive for its simple implementation using commercially available dimethoxytetrahydrofuran **70** as a four-carbon synthon.

4.2 Construction of dibenzofurans from phenol derivatives.

The synthesis of dibenzofurans by creating the benzofuran ring is poorly documented and represents a real challenge for the chemist. Takana proposed in 2009 a flexible synthesis of dibenzofurans and aza-dibenzofurans by rhodium-catalyzed [2+2+2] cycloaddition with phenol-linked 1,6-diynes and alkynes or enol ethers (Scheme 43).⁹² The authors demonstrated that cationic rhodium(I) associated with biaryl bisphosphine ligands catalyzed [2+2+2] cycloaddition

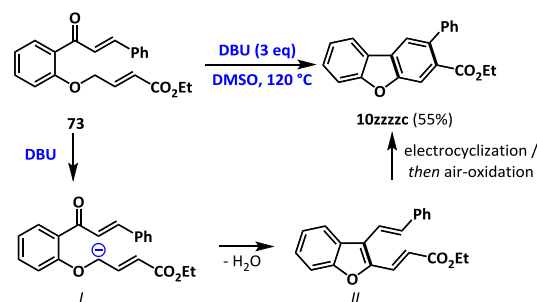
reactions with alkynes or enol ethers with nitriles derivatives to give respectively dibenzofurans and benzofuro[3,2-*c*]pyridines.



Scheme 43. Synthesis of tri-substituted dibenzofurans **10** from 1,6-diynes **71** and alkynes **72**.

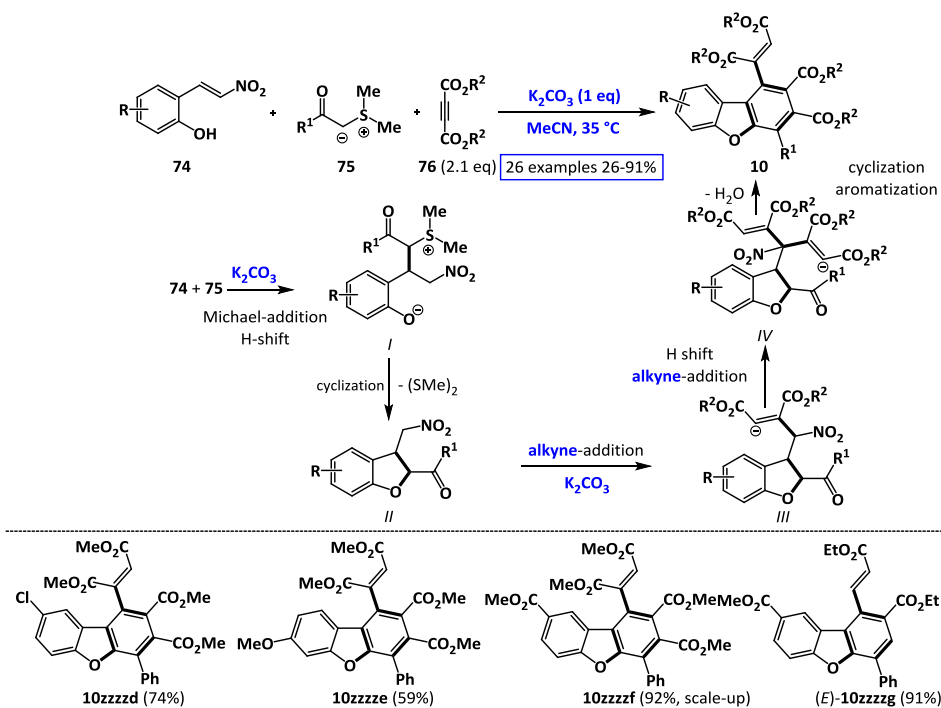
Oxidative addition of the rhodium catalyst to the triple bonds of **71** provides a rhodacyclopentadiene intermediate **I**, which inserts symmetrical alkyne **72** to give rhodacycloheptatriene intermediate **II**. Reductive elimination of the rhodium catalyst provides substituted dibenzofurans **10** and regenerates the rhodium catalyst. Notably, non-symmetrical alkynes were inserted with variable regioselectivities to give a mixture of regioisomeric dibenzofurans.

Sharma and Schlitzer proposed a metal-free synthesis dibenzofuran **10zzzzc** from chalcone **73** (Scheme 44).⁹³



Scheme 44. Metal-free synthesis of ethyl 2-phenyldibenzo[*b,d*]furan-3-carboxylate **10zzzzc**.

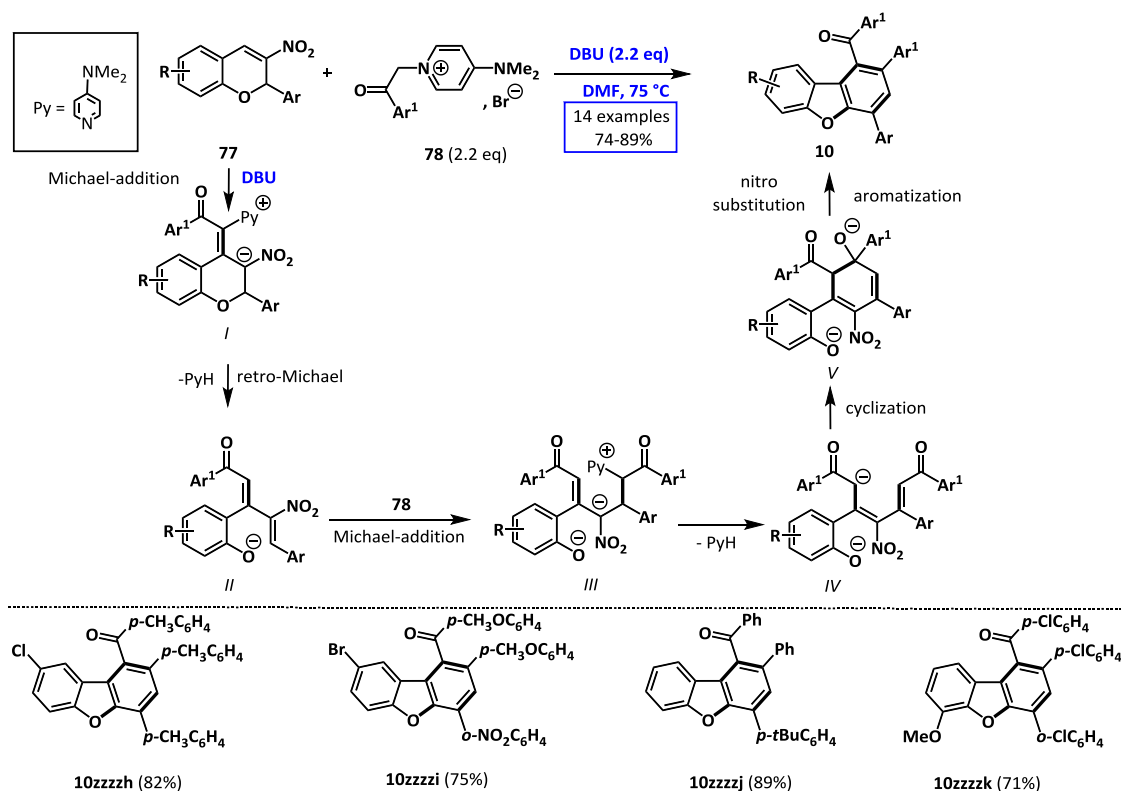
The mechanism starts by deprotonating 2-substituted chalcone **73** to give an anionic intermediate **I**. Adding the γ -anion on C=O creates the C–C bond of benzofuran intermediate **II** after a loss of water and aromatization. Then, benzofuran **II** can perform a 6π -electrocyclization followed by air oxidation to give dibenzofuran **10zzzzc** a yield of 55%. This metal-free process also efficiently prepares tricyclic heterocycles from substituted chalcones as carbazoles, benzo[*c*]coumarins, and phenanthridin-6(5H)-ones.



Scheme 45. One-pot synthesis of dibenzofuran acrylate derivatives **10**.

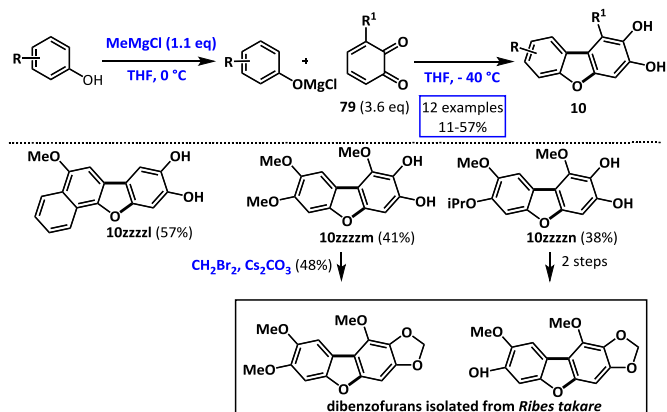
In a recent article, Shao and Chen reported a one-pot synthesis of poly-substituted dibenzofuran acrylate derivatives by reacting (*E*)-(2-nitrovinyl)phenols **74** with sulfur ylides **75** and acrylates **76** (Scheme 45).⁹⁴ First, the reaction was tested by mixing equimolar quantities of (*E*)-(2-nitrovinyl)phenols **74** and sulfur ylides **75**. Then, dimethylacetylene dicarboxylate (1 eq) and K₂CO₃ were added to give a complex mixture of dibenzofuran, having integrated one or two alkyne units. Unfortunately, the authors failed to avoid a second alkyne addition (see proposed mechanism below). They next focused on finding the best conditions to increase the yield of dibenzofurans with four ester functions using 2.1 eq of alkynes. The reaction tolerated well substituents of different natures. Electron-withdrawing groups (R = Cl, F, Br, CO₂Me) on the phenol ring were beneficial for the reaction. The reaction is also applicable with many sulfur ylides with 1-naphthyl, 2-naphthyl, 2-thienyl, cyclopropyl and electron-rich or electron-poor phenyl rings attached to the carbonyl. A scale-up experiment to **10zzzzf** was carried out with an excellent yield of 92%. The authors proposed a mechanism to explain the formation of these poly-substituted dibenzofurans. Schematically, a first Michael-addition of ylide **75** on nitroolefin **74** furnishes after H-shift a phenolate intermediate *I*, which cyclizes to give benzofuran *II*. A conjugate addition of anion *II* on alkyne **76** and H-shift furnishes a disubstituted dihydrobenzofuran *III*. This intermediate adds a second alkyne equivalent to provide a tricyclic intermediate of type *IV*. This intermediate undergoes an intramolecular cyclization by creating a fourth C-C bond, and an elimination process generates dibenzofurans **10**. The reaction also

worked well with ethyl acrylate to give regioselectively (*E*)-**10zzzzg**. A convenient synthesis of dibenzofurans resulting from a Michael-addition/Retro-Michael reaction/Michael-addition process was reported by Yan using 2-aryl-3-nitrochromenes **77** and 4-*N,N*-(dimethylamino)phenacyl pyridinium salt **78** in alkaline media (Scheme 46).⁹⁵ Yan studied the domino annulation reaction of 2-aryl-3-nitrochromenes **77** with pyridinium salt **78** in the presence of different bases (NEt₃, K₂CO₃, DABCO, and DBU) in a variety of solvents (EtOH, MeOH, toluene, THF, DMF, MeCN, and DMF). Best reaction conditions required to stir in hot DMF (75 °C) 2-aryl-3-nitrochromenes **77** with the pyridinium salt (2.2 eq) in the presence of DBU (2.2 eq). Substituents of different natures were well tolerated on the chromene ring and on both aryl groups of **77** and **78** (Ar and Ar¹) to furnish dibenzofurans **10** with good yields. The proposed mechanism evokes a first Michael addition of pyridinium ylide on 2-arylchromene **77**, giving a zwitterionic intermediate *I*, which can be isolated. This intermediate evolves according to a retro-Michael reaction, giving a phenolate intermediate *II* followed by a second Michael addition of the pyridinium ylide on *II*. Elimination of a proton and pyridine furnishes carbanion *IV*, which adds to carbonyl, affording the arene intermediate *V*. Finally, aromatization and nucleophilic substitution of the phenolate ion to nitro group^{42,43} gives dibenzofuran **10**. Interestingly, intermediate *IV* cyclizes rapidly and does not isomerize to give a regioisomer in which the -Ar¹ and -COAr¹ groups would be reversed.



Scheme 46. Synthesis of dibenzofurans **10** via domino reaction of coumarins **77** and pyridinium salts **78**.

In 2017, Barrow and Zhang created the benzofuran ring of dibenzofuran **10** from the reaction of phenols and *ortho*-benzoquinones **79** (Scheme 47).⁹⁶

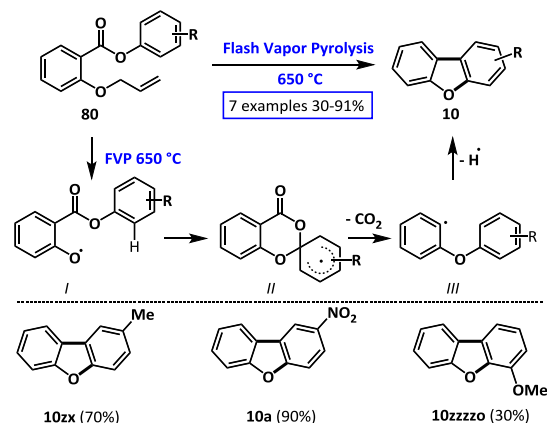


Scheme 47. Synthesis of poly-oxygenated dibenzofurans **10** from the reaction of phenolates with *ortho*-benzoquinones **79** and access to metabolites isolated from *Ribes takare*.

The authors found that MeMgCl was superior as a base to *n*BuLi or NaH in this process and proposed, to begin the process by deprotonating phenol substrates at 0 °C. After that, they added at -40 °C *ortho*-quinones **79** (3.6 eq), acting both as a Michael acceptor and as an oxidant in this process. The authors proposed a Michael/oxidation/oxa-Michael cascade to explain the reaction. Initial Michael reaction creates a C–C bond between the two aromatic rings. Then, after oxidation of the resulting catecholate anion by *ortho*-quinone **79**, an oxa-Michael addition creates the C–O bond of dibenzofurans⁹⁷ with moderate yields. The synthetic

utility of this cascade reaction was highlighted through the synthesis of two dibenzofurans isolated from *Ribes takare*, a deciduous shrub widely distributed in China, Bhutan and India of the genus *Ribes*.⁹⁸

Cadogan and McNab proposed in 2010 to form dibenzofurans by flash vacuum pyrolysis of aryl 2-(allyloxy)benzoates **80** (Scheme 48).⁹⁹ Flash pyrolysis of 2-(allyloxy)benzoates **80** achieved at 650 °C worked well with *para*-substituted substrates, (e.g. **10zx**, **10a**), unlike *ortho*- or *meta*-substituted substrates which gave mixture of dibenzofurans, which could be separated. The authors proposed a radical mechanism that starts with the formation of a phenoxy radical **I** after homolysis of the *O*-allyl bond.



Scheme 48. Flash pyrolysis of aryl 2-(allyloxy)benzoates **80**.

Then a spirodienyl radical **II** is generated after creating a new C–O bond. Decarboxylation of **II** furnishes an aryl radical **III** is formed

which cyclizes to provide the dibenzofuran. This process also efficiently synthesizes dibenzothiophenes from aryl 2-(allylthio)benzoates but seems limited to robust substrates.

5. CONCLUSION

In conclusion, through around 120 references, we have seen about fifty different approaches giving access to the dibenzofuran core identified over the past 15 years. Due to the presence of this nucleus in natural products, pharmaceuticals and photo-

luminescent materials, there has been a genuine interest to synthesize this heterocycle by modern methods in recent years. In most cases, syntheses of dibenzofurans with biological or photovoltaic properties begin with creating the dibenzofuran unit, which is then functionalized.¹⁰⁰ With this in mind, we think simpler to synthesize this heterocycle by first creating the C–O bond or the C–C bond of the central 5-membered ring (Sections 2 and 3). Figure 10 shows a selection of some methodologies used recently to prepare substituted dibenzofurans bearing electron-withdrawing and electron-donating groups by forming a C–O bond or a C–C bond. These approaches requiring mainly catalytic methodologies allow fast access to compounds of simple structure in environmentally acceptable experimental conditions.

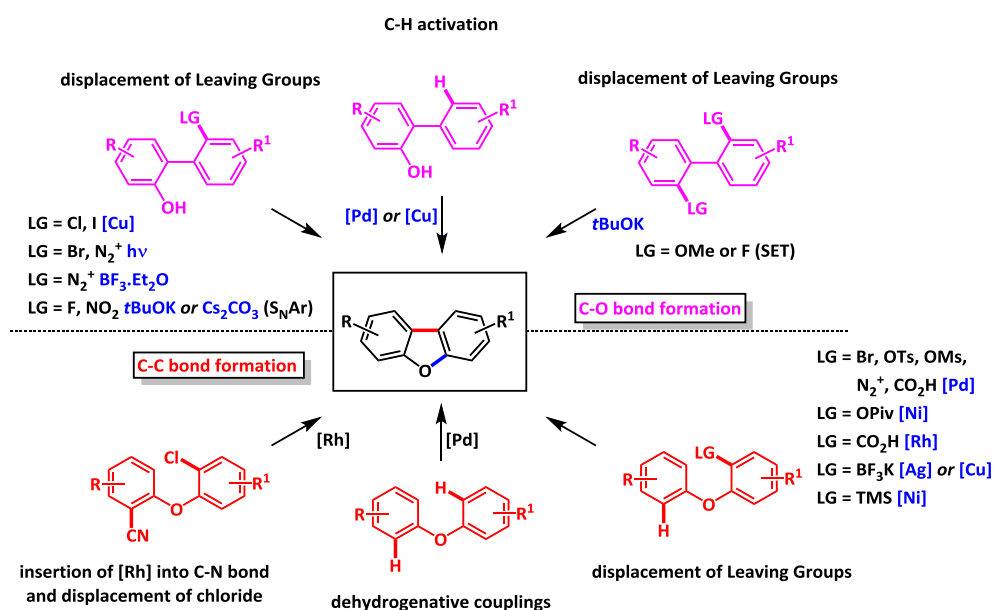


Figure 10. Recent accesses to dibenzofurans by forming the furan ring.

However, few examples of *meta*-substituted aromatic derivatives as starting substrates have been described for methodologies using C–H activation¹⁴ probably due to the lack of regioselectivity of cyclization reactions. It might be interesting to cyclize (*o,m*)-disubstituted compounds and remove a labile *o*-substituent, only used to direct the cyclization reaction. As we mentioned in Section 4, the synthesis of dibenzofurans from benzofurans or phenol derivatives has grown considerably in recent years, providing access to specific poly-functionalized compounds. These methods are desirable since they enable the creation of several bonds in a single step. For example, electron-rich benzofurans react with various electrophiles or alkylidene malonitriles to give the expected dibenzofurans by creating two C–C bonds. Very often, benzofurans are previously functionalized before being transformed into dibenzofurans *via* 6π-electrocyclization reactions. The creation of variously substituted dibenzofurans from phenol derivatives is

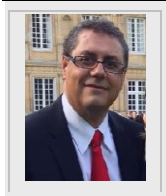
rarely studied and involves, for example, Michael reactions followed or not by cyclization reactions. We hope this update will enable chemists interested in dibenzofurans to rapidly prepare this type of heterocycle or propose other general or specific access via totally "green" processes.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This review is dedicated to Pr. G. Lhomme for his advances in heterocyclic chemistry.



Dr. Mouad Alami is a Research Director at the CNRS (Faculty of Pharmacy, BioCIS, France). He did his PhD at UPMC in Paris (1987), and after two years of post-doctoral position in collaboration with the Elf-Atochem company, he joined in 1989 the CNRS at the ENS-Paris (Dr. G. Linstumelle). In 1993, he spent one year at the University of Santa-Barbara (Pr. B.H. Lipshutz). In 1999, he became CNRS Research Director at the Faculty of Pharmacy (University Paris-Saclay). His fields of specialization include (i) development of novel selective synthetic methodologies involving organometallic chemistry and (ii) synthesis of structurally challenging and biologically relevant products with antitumoral activity.



Dr. Olivier Provot was born in 1963 in the beautiful city of Caen (Normandy, France) and received his PhD in total synthesis of antivenom (Pr. G. Lhomme in 1991, UPMC, Paris VI). After two post-doctoral positions in industry and at the Lab of Medicinal Chemistry (University Paris VII), he moved to the University of Paris-Sud to start his independent research on syntheses of natural peroxides having antimalarial activities. He completed his habilitation in 1999 and joined in 2003 the group of Dr. M. Alami (University Paris-Saclay). His research is focused on the development of organometallic methodologies (Pd, Pt), green accesses to various heterocycles. All of these processes are applied to the synthesis and evaluation of anti-cancer drugs related to Combretastatin A-4 (> 100 publications, 10 patents).

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