O-Annulation Leading to Five-, Six-, and Seven-Membered Cyclic Diaryl Ethers Involving C–H Cleavage

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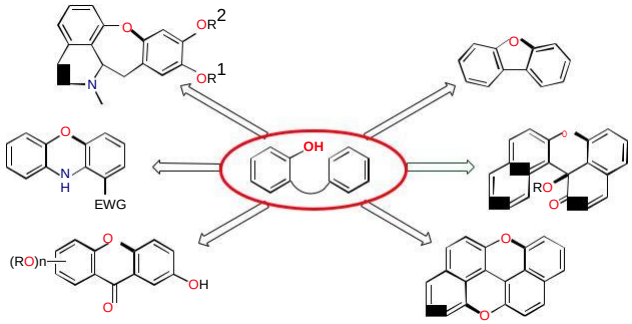

Abstract Cyclic diaryl ethers are present in multiple natural compounds, organic pollutants as well as in -conjugated organic molecular materials. This short review aims at overviewing the main synthetic ad-vances in the O-annulation methods for preparing five-, six-, and seven-membered rings through C–H cleavage.

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Key words cyclic diaryl ether, oxidative cyclisation, cycloetherification, C–H activation, C–O bond formation, O-annulation, pyrans, furans, cularine

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1 Introduction

Cyclic diaryl ether motifs are found in a large variety of organic molecules, spamming from natural products to polycyclic aromatic hydrocarbon (PAHs) structures (Figure 1). The antibiotic drug Vancomycin is probably the most fa-mous structure.[1a] Other examples include Vicanicin, a li-chen second metabolite depsidone exhibiting antitumor ac-tivity,[1b] and Asterelin A, an antifungal drug (Figure 1, top).[1c]

Concerning artificial cyclic ethers, the polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans are certainly the most infamous examples, being in the 'Dirty Dozen' list of Persistent Organic Pollutants (POPs) (Figure 1, centre).[2] Cyclic ethers also constitute the core of O-doped

polycyclic aromatic hydrocarbons (PAHs), a class of elec-tron-rich aromatics used to engineer organic semiconduc-tors (Figure 1, bottom). For instance, derivatives of Pum-merer's *peri*-xanthenoxanthene (PXX) have been used as organic semiconductors for engineering the first Sony's 'Rollable OTFT-driven OLED that can wrap around a Pencil'.[3] 2*H*-Pyran-based dithienopyran (DTP)[4] and dibenzopyran (DBP)[5] motifs were introduced as the electron-donating moiety in donor-acceptor (D–A) type conjugated copoly-mers to engineer solar cells with high power conversion ef-ficiencies (PCEs). Molecular units based on 9-[3-(diben-zo[*b*,*d*]furanyl)phenyl]-9*H*-carbazole (DFPCz) scaffold have been used as organic phosphors in PHOLEDs.[6]

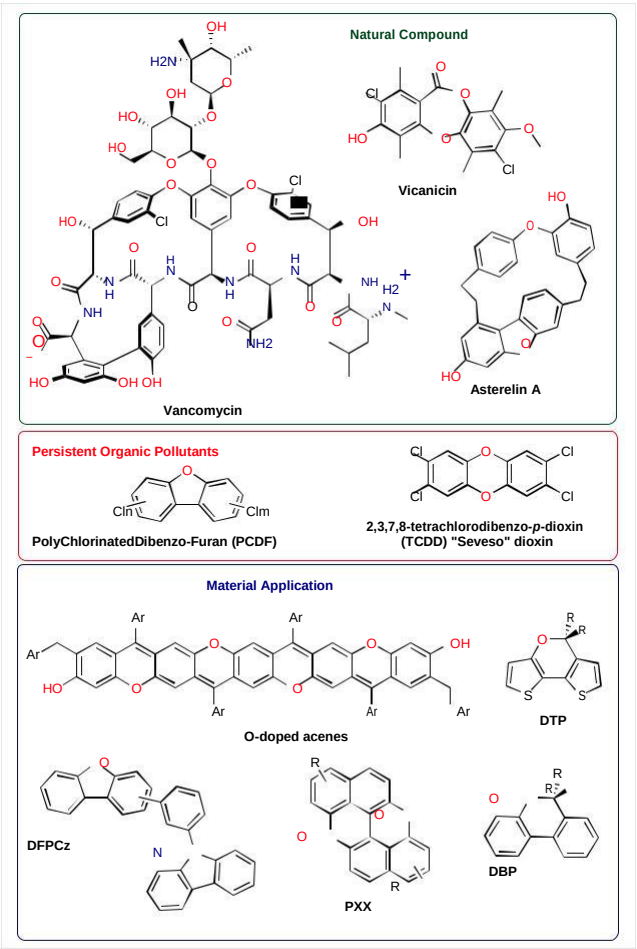
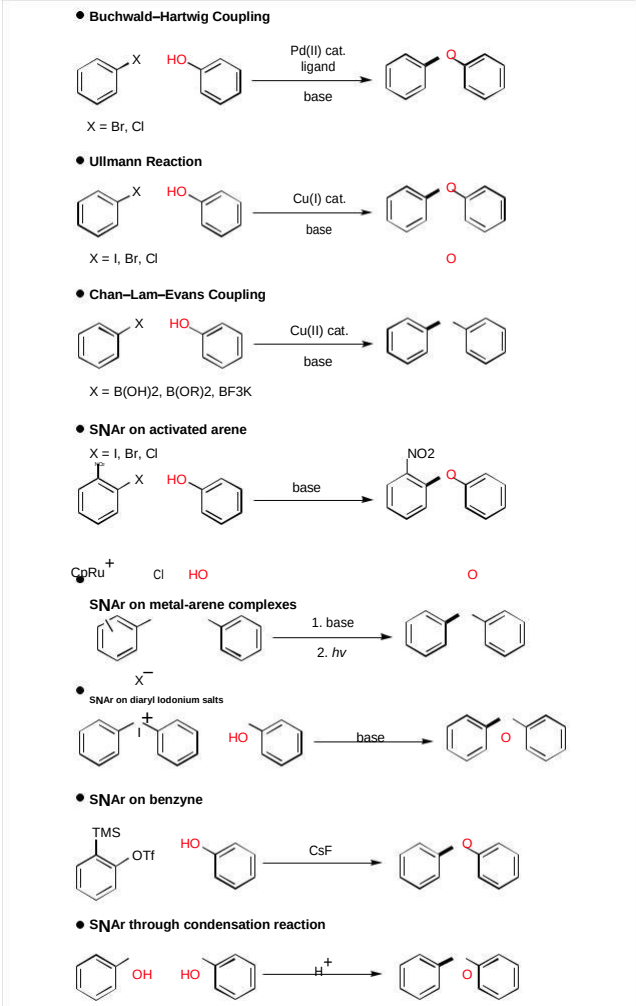


Figure 1 Examples of natural and artificial products featuring cyclic ether structural motifs

Very interesting *p*-type organic semiconductor based on O-doped quinoidal pentacenes and nonacenes were recent-ly prepared following a cross-condensation route.[7] At the synthetic planning level, cyclic diaryl ethers are usually pre-pared through an intramolecular coupling reaction be-tween a phenol moiety and a pre-functionalized aryl sub-strate. In particular, two routes have been mostly exploited: (*i*) transition-metal-catalysed C–O cross-coupling reactions (i.e., Buchwald–Hartwig,[8] Ullmann etherification,[9] and Chan–Lam–Evans[10] coupling), and (*ii*) nucleophilic aromatic substitution reactions.[11,12] Both synthetic approaches rely on the use of electrophilic aromatic halides or strong acidic conditions to ensure the 'activation' of the aryl substrate and control the regioselectivity of the addition reaction (Scheme 1).



Scheme 1 General methodologies for preparing diaryl ethers

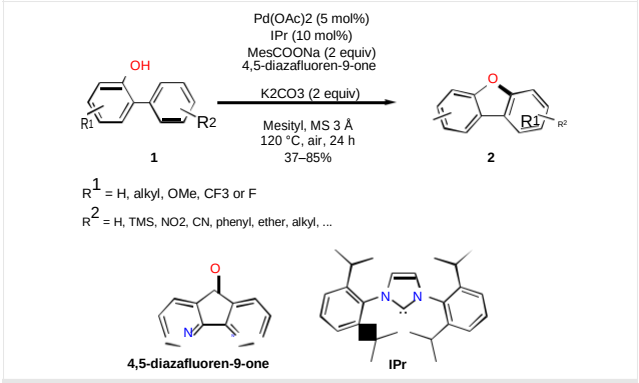
Also, the electrophilic partner needs to be pre-function-alised at a given position with electron-withdrawing groups (EWGs) and undergoes metal-arene formation,[13] di-aryl iodonium salt,[14] and in situ formation of benzyne spe-cies[15] to favour the relevant addition reaction (Scheme 1). Cross-condensation reaction promoted by strong acids is also a valuable route when the substrate is not acid-sensi-tive.[16] The interested reader can refer to recent reviews tackling these synthetic routes.[17] A more attractive route would involve the formation of a cyclic diaryl ether through direct C–H functionalisation of an aryl substrate with a giv-

en phenolic moiety. It is with this aim that in this review paper we describe the recent synthetic developments tackling the formation of cyclic diaryl ethers using an intramolecular etherification route involving a C–H cleavage reaction. This review will provide an exhaustive picture of the synthetic plans involving the specific reactions and substrates to give five-, six-, and seven-membered rings.

2 Five-Membered Rings: The Dibenzofuran (DBF) Motif

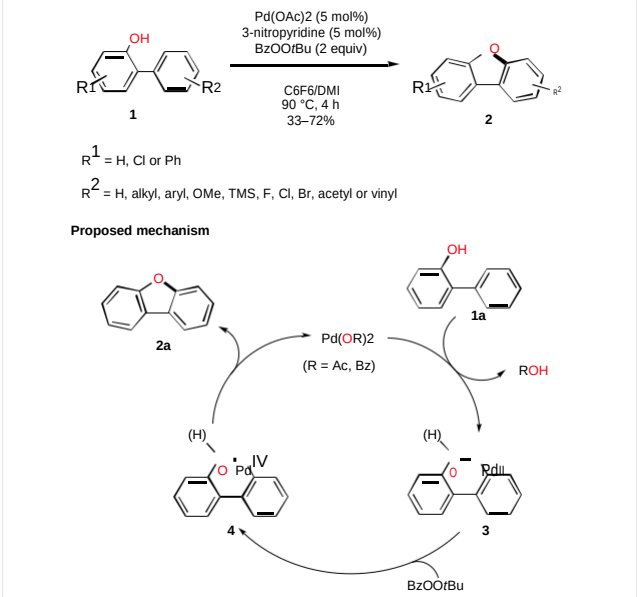
2.1 Palladium-Catalysed C–H Activation

In 2011, Liu and co-workers[18] described the first transition-metal-catalysed cyclisation reaction involving a C–H activation/C–O bond formation to obtain dibenzofuran derivatives by aerobic oxidation starting from 2-phenylphenol **1**. Their method involves the use of $Pd(OAc)_2$, 1,3-bis(2,6-di-isopropylphenyl)imidazole-2-ylidene (IPr), mesitylene carboxylate (MesCOONa), 4,5-diazafluoren-9-one as ancillary ligands, and K_2CO_3 (Scheme 2). The use of the anionic ligand MesCOONa serves as a proton shuttle to promote C–H activation and 4,5-diazafluoren-9-one to favour the aerobic oxidation of the Pd(0)-based species to active Pd(II) complex-es. Substrates bearing electron-donating groups (EDGs: amine, ether, ketal, and silyl) as well as electron-withdraw-ing groups (EWGs: cyano, ketone, nitro, amide, ester, sul-fonamide, fluoride, chloride, and trifluoromethyl) on both the aryl and phenol moieties were used. Kinetic isotope ef-fect (KIE) investigations suggested that the rate determining step is the C–O reductive elimination. Moreover, the reac-tion occurs quantitatively and regioselectivity at the least sterically hindered C–H positions.



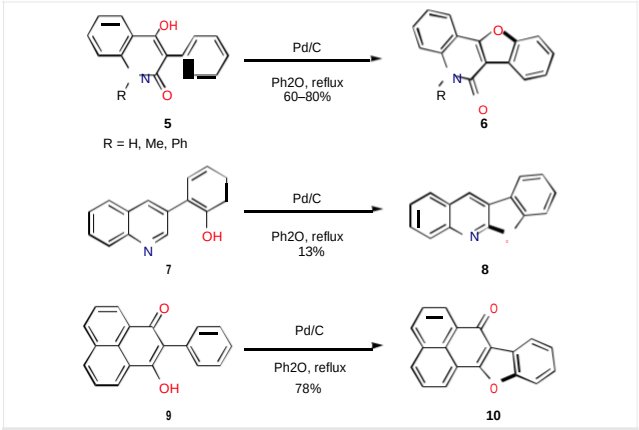
Scheme 2 Palladium-catalysed DBF formation reported by Liu and co-workers[18]

In parallel, Wei and Yoshikai[19] developed a base-free method using $Pd(OAc)_2$ and 3-nitropyridine as the ligand (Scheme 3). Under these conditions, aerobic oxidation is inefficient and BzOO*t*Bu was used as an inexpensive oxidant for the regeneration of the active palladium species. Mix-ture of aromatic and Lewis-basic solvents, such as C_6F_6 and DMI (1,3-dimethyl-2-imidazolidinone) (3:2 ratio), gave the highest yield. With respect to Liu's Pd-catalysed cycloether-ification reaction, in this case, KIE investigations suggests that the rate determining step is the C–H bond cleavage (k_H/k_D = 1.9). Building on these kinetic studies, and consid-ering that BzOO*t*Bu is a stronger oxidant than O_2, the au-thors suggested that the reaction is initiated by a C–H bond cleavage through the formation of pallada(II)cycle interme-diate **3**. The latter is subsequently oxidised by BzOO*t*Bu to give pallada(IV)cycle **4**. The latter intermediate can reduc-tively eliminate a Pd(II) specie, forming the C–O bond, and yielding dibenzofuran **2**. As described for the reaction above, also in this case the C–O bond formation occurs at the least sterically hindered position. Notably, substrates bearing either EWGs or EDGs tolerate the oxidative reaction conditions. Building on this work, Schmidt and Riemer[20] re-cently described a microwave-promoted cyclisation proto-col, in which oxidative C–H activation using catalytic amounts of $Pd(OAc)_2$ could be used to prepare DBFs. The re-action works under water-free conditions in non-protic sol-vents such as benzene and ethereal solvents (THF, MTBE, DME, or DDME).



Scheme 3 Pd-catalysed DBF formation reported by Wei and Yoshikai[19]

In 1980, Kappe and co-workers presented a non-CH activated Pd-catalysed diaryl ether formation relying on cyclodehydrogenation of 4-hydroxy-3-phenylquinolinone **5**, quinolinylphenol **7**, and hydroxyphenylphenalenone **9** to prepare the corresponding furan derivatives **6**, **8**, and **10** (Scheme 4).[21] This method was further used to synthesise biologically active benzofuroquinolinone.[22]

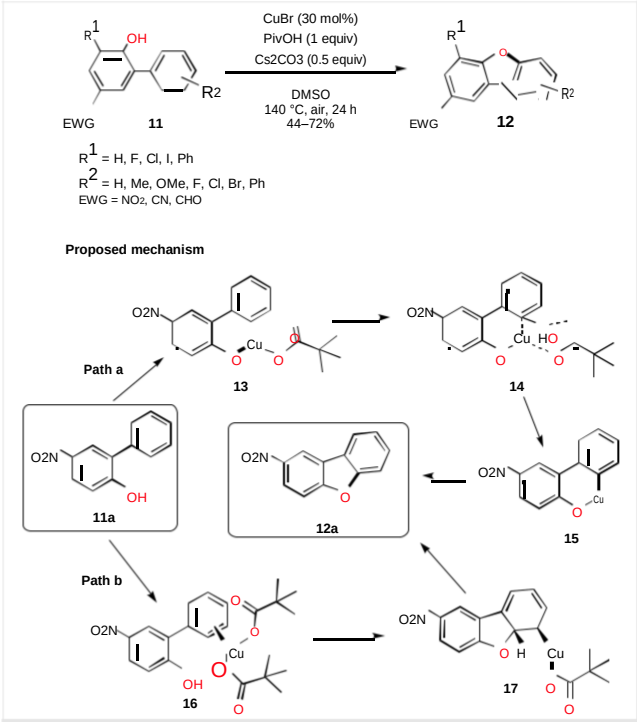


Scheme 4 Palladium-catalysed cyclodehydrogenation for the forma-tion of benzofuranes as developed by Kappe and co-workers[21]

2.2 Copper-Mediated C–H Activation

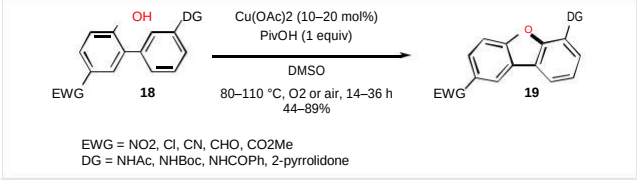
In 2012, Zhu and co-workers published three papers on the dibenzofuran synthesis through C–H bond cleavage/C– O bond formation using Cu-based catalysts.[23–25] The use of copper is more convenient compared to other transition metals as it is considerably cheaper and compatible with O_2. However, the presence of relatively strong EWGs on the phenolic ring (e.g., nitro, cyano, and carbonyl groups) is re-quired to overcome undesired homocoupling of phenols or other side-reactions usually promoted by copper. In the first protocol, CuBr was used (30%) in the presence of Cs_2-CO_3, and pivalic acid in the air (Scheme 5).[23] Notably, *ortho*-functionalised substrates did not allow formation of the C– O bond, whereas the *meta* congeners gave the cyclised products with a 20:1 regioselective ratio toward the least sterically hindered isomer. For substrates bearing bulky substituents such as I or Ph, $Cu(OAc)_2$ was used to avoid the formation of undesired brominated by-products. As men-tioned above, the phenolic ring can only bear EWGs, where-as the phenyl ring tolerates both EWGs and EDGs.

Together with a KIE value of 4.5, the absence of proton scrambling suggested that the C–H bond cleavage is the rate determining step. As studies with competitive reactions be-tween electron-rich and -poor aryl substrates did not give any conclusive results, the authors suggested that the cycli-sation reaction could result from either a concerted metala-tion deprotonation (CMD) mechanism or an electrophilic substitution (Scheme 5, paths a,b, respectively). A radical pathway was excluded as the reaction is not affected by the presence of a radical scavenger such as TEMPO. As there are no evidences for the Cu(II)/Cu(0) couple involvement, the oxidative Cu(III)/Cu(I) cycle could not be completely exclud-ed. In a subsequent work,[24] the same authors reported on the development of an efficient Cu-catalysed oxidative C–O bond formation of electron-deficient *ortho*-phenols con-taining supplementary directing *meta*-groups (e.g., NHAc , NHCOPh, 2-pyrrolidone, and NHBoc) on the non-phenolic



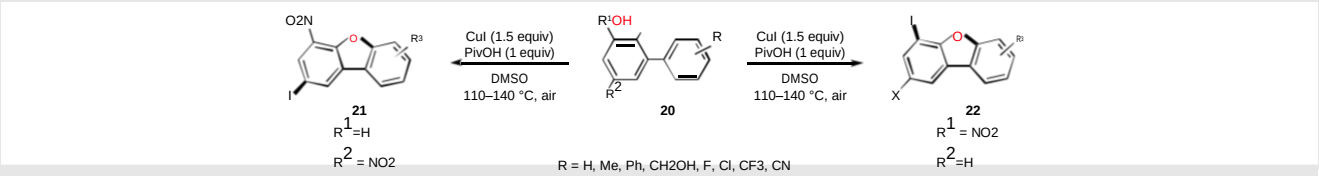
Scheme 5 Cu-catalysed DBF formation reported by Zhu and co-work-ers.[23] Proposed mechanistic pathways: (path a) concerted metalation deprotonation and (path b) electrophilic metalation.

ring. Together with the hydroxy group, the amidic carbonyl functional group chelates the copper metal centre allowing the reaction to be performed without a base and at low temperatures. Notably, high yields (up to 99 %) and a broad substrate scope with full control on the regioselectivity could be achieved with these substrates (Scheme 6). In a later work, Zhu and co-workers reported the first example of a sequential iodination-cycloetherification reaction of *o*-arylphenols mediated by CuI in the presence of O_2.



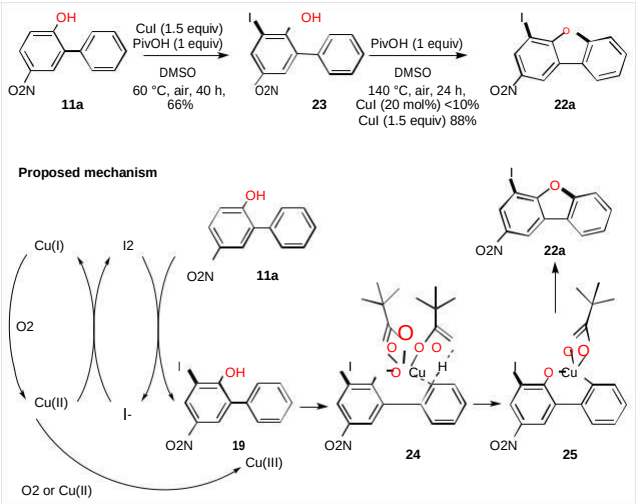
Scheme 6 Cu-catalysed DBF formation reported by Zhu and co-work-ers[24]

This permitted the synthesis of 2- and 4-iododibenzofu-rans derivatives using CuI as both iodinating agent and cat-alyst for the C–H activation/C–O bond formation. Iodination of the phenolic ring at either the *ortho* or *para* positions de-pending on the position of the EWG was observed (Scheme 7).[25] Notably, a thermal control of the iodination reaction to occur prior to the C–O cyclisation could be obtained. Heat-ing the reaction mixture at 60 °C gave first the iodo-inter-



Scheme 7 Cu-catalysed DBF formation reported by Zhu and co-workers[25]

mediate that, at 140 °C, could be cyclised into the furanyl derivatives in the presence of a stoichiometric amount of CuI (Scheme 8).

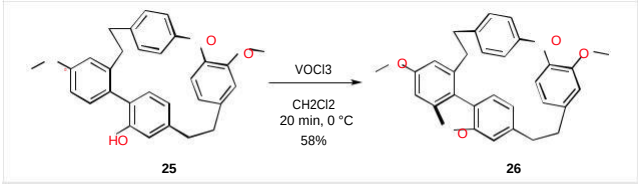


Scheme 8 Sequential Cu-catalysed iodination and C–O cyclisation re-ported by Zhu and co-workers.[25]

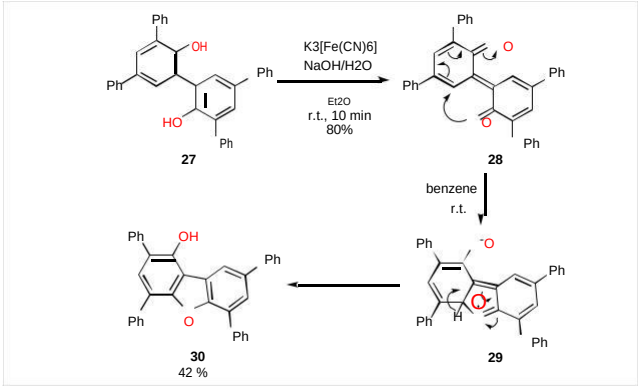
This reaction tolerates EWGs (e.g., Cl, F, CF_3, NO_2, CN, and CHO) and EDGs (e.g., Me, OMe, and Ph). Notably, replacing the CuBr with CuI, the corresponding brominated product could be obtained. As in all cases discussed above, the reaction occurs at the least hindered position (regioselectivity 5:1). Capitalising on KIE experiments (4.1) and mechanistic studies using DFT calculations, the authors suggested that the reaction occurs through a pivalate-as-sisted CMD pathway (Scheme 8) initiated by Cu(III) species. Single electron transfer (SET) or electrophilic aromatic sub-stitution (S_EAr) mechanisms were excluded.

2.3 Non-CH Activation Oxidant-Mediated Cyclisa-tion

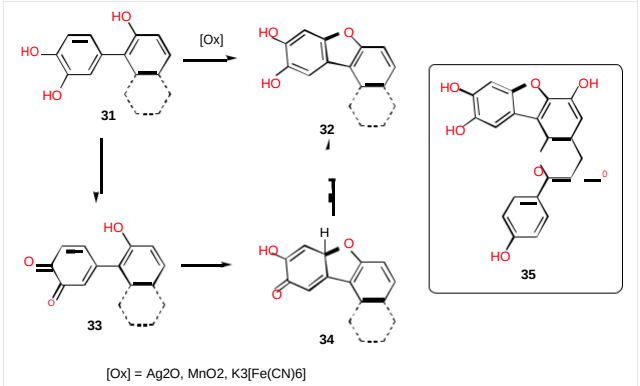
Other convenient synthetic methods to form furan cycles include oxidation methods that do not involve any direct C–H activation, such as (*i*) transition-metal-free oxidative cyclisations of phenolic ring and trapping of the reactive intermediate by an hydroxyl group[26] (Scheme 9), (*ii*) intramolecular cyclisation of 2,2′-biphenoquinone[27] (Scheme 10), and (*iii*) oxidation/oxa-Michael cascade reaction (Scheme 11). The latter method relies on the oxidation of a pyrocatechol moiety **31** to the corresponding 1,2-benzoquinone **33**. Subsequent intramolecular 1,4-addition of the neighbouring hydroxyl groups, followed by a tautomerisation/rearomatisation reactions, gave dibenzofuranes **34** and **32**, respectively (Scheme 11). Commonly used oxidants for this transformation are Ag_2O,[28] MnO_2,[29], and $K_3[Fe(CN)_6]$.[30] Capitalising on this reaction, Lu and co-workers prepared derivative **35**, an important intermediate for the total synthesis of (±)-anastatins A and B (Scheme 11).[31]



Scheme 9 Synthesis of asterelin A by Makino et al. involving an oxida-tive cyclisation[26]



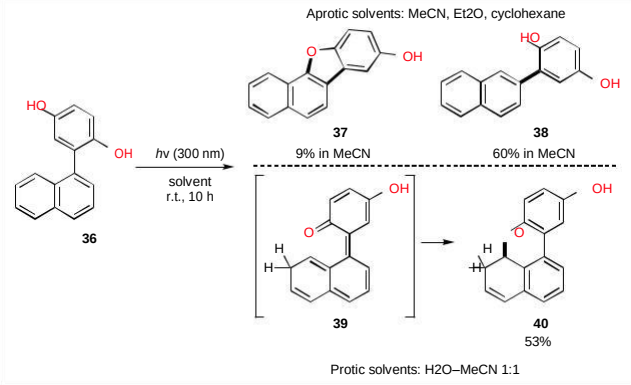
Scheme 10 Proposed mechanism by Hayashi et al. for the intramolec-ular cyclisation of tetraphenyl-2,2′-benzoquinone[27]



Scheme 11 General oxidative formation of DBF through quinone for-mation (left) as reported by Lu and co-workers[31]

2.4 Light-Mediated Cyclisation

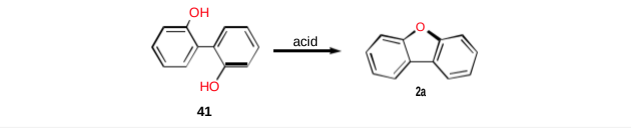
The formation of dibenzofurans was also obtained by photoirradiation of phenols precursors through Excited State Intramolecular Proton Transfer (ESIPT). For example, Wan and co-workers[32] observed the formation of diaryl furans in low yield (2–9%) when 1-(2,5,dihydroxyphenyl)naphthalene (**36**) was exposed under irradiation at 300 nm. Notably, different products were obtained depending on the solvent polarity. For instance, in aprotic solvents, a predominant C–C bond migration was observed yielding 2-(2,5-dihydroxyphenyl)naphthalene (**38**) and naphthobenzofuran-8-ol (**37**) as the major (60% yield) and minor (9% yield) products, respectively. In protic solvents, an intramolecular proton transfer followed by electrocyclic ring closure was instead observed, with dihydrobenzoxanthene **40** (53% yield) being the only product (Scheme 12). Molecule **40** can undergo further oxidation to give the pyran derivative.



Scheme 12 Light-induced oxidative formation of DBF motifs[32]

2.5 Acid-Catalysed C–O Cleavage/C–O Formation

Biphenol **41** can be transformed into dibenzofuran **2a** through C–O cleavage/C–O formation, likely following a SEAr mechanism (Scheme 13). This reaction is usually carried out in the presence of either strong Brønsted acids[33–35] (e.g., PTSA, TfOH, H_2SO_4, and HBr), Lewis acids[36] (e.g., $SnCl_4$, Al_2O_3, and zeolite) or noble metal surfaces [e.g., Au(111) and Ag(111)].[37] The latter method has been largely reported in the literature for the preparation of organic materials such as O-doped graphenes[37] and helicenes.[38]



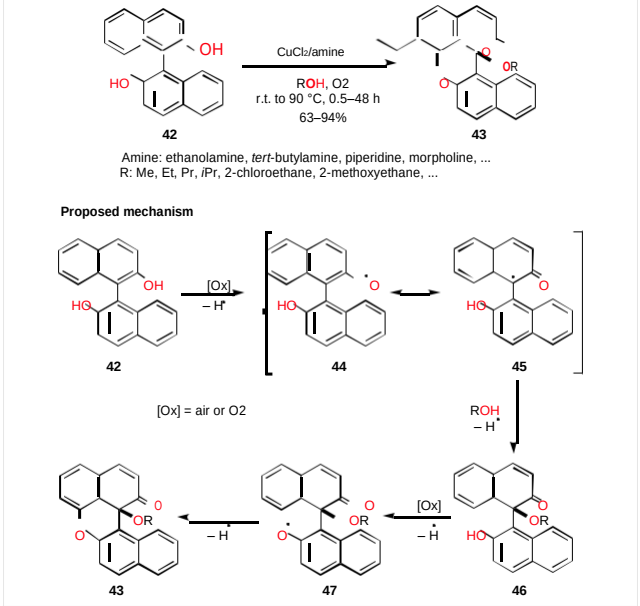
Scheme 13 Formation of DBF from 2,2′-biphenol

3 Six-Membered Rings: DBX, PXX, Xanthone, and Their Derivatives

Concerning the six-membered cyclic ethers, these can be classified as: (*i*) dibenzoxanthene (DBX), (*ii*) *peri*-xanthe-noxanthene (PXX), (*iii*) xanthones (presenting a carbonyl group joining both aromatic cycles), (*iv*) miscellaneous de-rivatives featuring both five- and six-membered rings, and (*v*) phenoxazines.

3.1 Dibenzoxanthene (DBX)

The first synthetic protocol for the preparation of dibenzoxanthenes (DBX) **43** from a tetra-*tert*-butylated BINOL derivative was developed in 1963 by Rieche et al.,[39] and later optimised by Schneider et al.[40] Their methods use $K_3[Fe(CN)_6]$ yielding DBXs in 38%. In 2001, Xu et al. discovered the almost quantitative formation of DBX using Cu(II)-amine complexes in hot MeOH in the presence of air.[41] This method tolerates a large variety of amines with the highest reaction rate observed when using ethanolamine. More-over, modification of the alcoholic solvent leads to a variety of derivatives bearing different alkyl ether functionality (Scheme 14). Racemic mixture was obtained when a chiral amine was used or optically pure BINOL was selected as starting material. Based on this observation, they proposed a mechanistic pathway involving the oxidation of BINOL **42** to naphthoxy radical **44**, which is in equilibrium with its carbon-centred radical analogue **45**. The latter radical can be trapped by the alcoholic solvent forming -alkyloxy ke-tone **46**, which could be further oxidised to form DBX **43** (Scheme 14). Later, this synthetic method was used for the



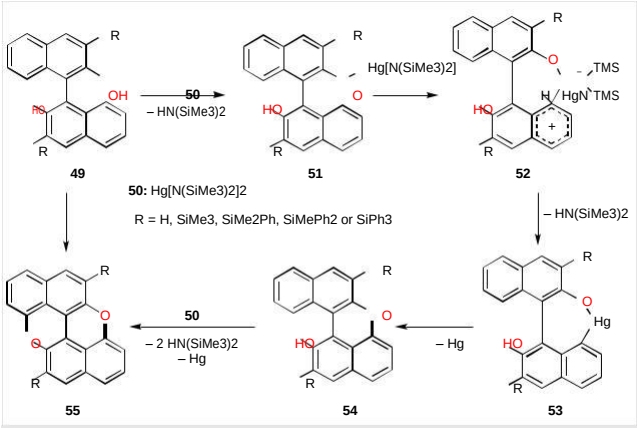
Scheme 14 Oxidative formation of DBX from BINOL[41]

synthesis of cancer drugs[42] or isolated as side product during the deracemisation of BANOL, a phenanthrene derivative of BINOL.[43]

3.2 *Peri*-Xanthenoxanthene (PXX)

The first synthesis of PXX dates back to the beginning of the 20th century when Bünzly and Decker[44] described the oxidation of BINOL in the presence of $K_3[Fe(CN)_6]$. Shortly after, Pummerer used Ag_2O, CuO, and $Cu(OAc)_2$ for the same transformation.[45] In 2001, Tamotsu and co-workers[46] revis-ited Pummerer's protocol, with $Cu(OAc)_2$ in aqueous alka-line solution (Table 1).

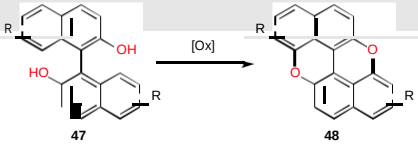
In 2007, Weinert and co-workers studied the oxidation of 3,3′-disubstituted BINOL in the presence of a sterically encumbered mercury salt, ($Hg[N(SiMe_3)]_2$) (**50**).[47] Depend-ing on the equivalent of oxidant involved in the reaction, they were able to isolate monopyranyl pentacyclic **54**. Based on ^1H and ^{199}Hg NMR, they have proposed a mecha-nistic pathway involving a mercuration reaction of the hy-droxyl groups followed by intramolecular electrophilic aro-matic substitution and extrusion of elemental Hg (Scheme 15). Following these reports, Cui and co-workers recently developed an improvement of the synthesis of PXX using $Cu(OAc)_2$ in *ortho*-dichlorobenzene at 190 °C under micro-wave irradiation for only 3 minutes.[48] In 2016, our group re-ported the synthesis of PXX and PXX-analogues[49] by adapt-ing Zhu's protocol for dibenzofuran. Specifically, CuI and pivalic acid in DMSO at 140 °C were used. Song and Swager also reported on the electrochemical cyclisation of BINOL derivatives to yield PXX-thiophene-based conducting poly-mers.[50] The last to date synthetic protocol for the cyclisation of BINOL to PXX relies on the use of CuCl with *N*-methylimidazole and K_2CO_3 as a base in hot *m*-xylene.[51] This method allows not only the formation of PXX at lower temperature, but to perform cascade dimerisation/cyclisation of simple naphthols. Similarly, Fuchs and co-workers used on-surface protocols to produce DBF- and/or PXX-polymers from 6,6′-dibromo-BINOL derivatives.[37]



Scheme 15 Proposed formation mechanism for PXX by Weinert and co-workers[47]

Building on the Cu-based protocols, our group could achieve the synthesis of extended PXX derivatives. In par-ticular, O-doped armchair **56**, **57**[49] and zig-zag **58** [52] molecu-lar ribbons, coloured -extended PXX **59** and **60**,[35] and monoimide(PXXMI)/diimide(PXXDI) derivatives **61** and **62**

Table 1 Oxidative Formation of PXX from BINOL



Reaction conditions:

Year	Reagents	R	Solvent	Temp/Time	Yield
1905[44]	$[K_3Fe(CN)_6]$	H	–	–	–
1914[45]	Ag_2O	H	benzene	80 °C/1 h	–
1914[45]	$Cu(OAc)_2/CuO$	H	$PhNO_2$	280 °C/3 h	52–80
2001[46]	$Cu(OAc)_2$	H	aq NaOH	r.t./1 h	–
2007[47]	$Hg[N(SiMe_3)]_2$	H, silyl	benzene	85 °C/24 h	49–97
2013[48]	$Cu(OAc)_2$, O_2	*n*-octyl	ODCB, pyridine	190 °C MWI/3 min	44–56
2016[49]	CuI, PivOH, O_2	2,4-di-*t*BuPh	DMSO	140 °C/2 h	94
2009[50]	$NOBF_4$	thiophene	CH_2Cl_2	r.t./6 h	42–78
2017[51]	CuCl, NMI, K_2CO_3, air	H, TMS, alkyl, aryl, CO_2Me, allyl	*m*-xylene	120 °C/20 h	55–99

were synthesised by our group (Figure 2).[53] In-depth photophysical and electrochemical studies revealed that all pyranopyran derivatives feature strong electron-donating properties due to their high-lying energy HOMO levels.[52,53] In particular, PXX, PXXMI, and PXXDI revealed to be strong photoreducers, with PXX featuring the same photoreducing potential as that of the commonly used Ir(III) complexes.[53a]

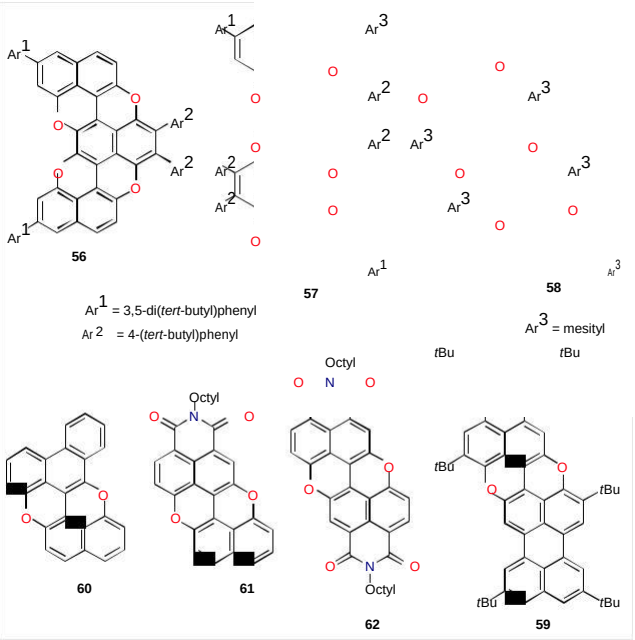


Figure 2 Chemical structures of extended PXX-based molecular archi-tectures

3.3 Xanthones

Being xanthones (i.e., 9*H*-xanthen-9-ones) important building blocks constituting various pharmacological activ-ities, they have been at the centre of a lot interest in syn-thetic organic chemistry.[54] For example, Norathyriol is a chemopreventive agent that is effective against skin can-cer.[55] Daviditin A is used to relax the corpus cavernous smooth muscle, while its Bellidifolin congener is a potent hypoglycemic regulator, improving insulin resistance.[56] Fi-nally, Atroviridin exhibits anti-inflammatory activity and is traditionally used for the treatment of earache (Figure 3).[57] In this regard, research groups have focused on the synthet-ic methodologies that use biogenetic-type approaches to perform the oxidation of the benzophenone core **63**. Poly-hydroxylated and methoxylated derivatives were common-ly used as substrates and treated with various oxidants such as $K_3Fe(CN)_6$,[58–61] CrO_3,[59] *p*-chloranil,[59] $KMnO_4$,[59,60] $K_2S_2O_8$,[60] $Mn(OAc)_3$,[61] $Pb(OAc)_4$,[61] and silver salts[62] (Scheme 16).

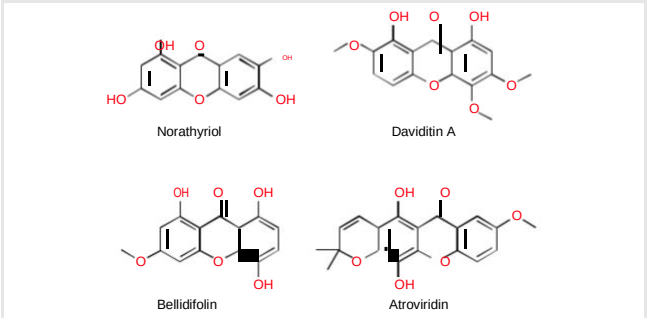
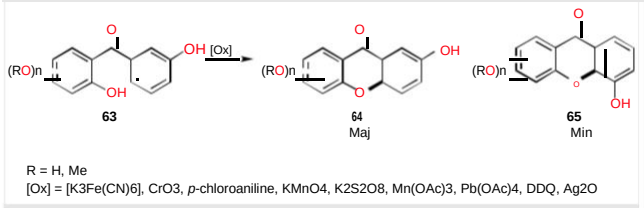
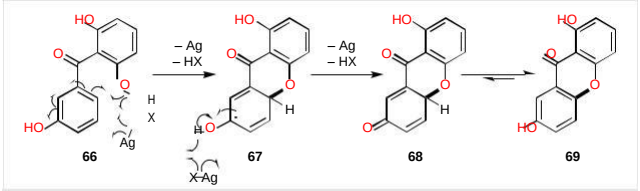


Figure 3 Examples of biologically active xanthones



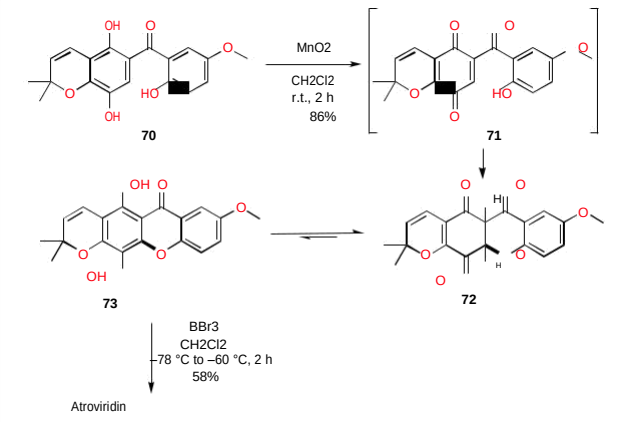
Scheme 16 Formation of xanthone by oxidation of polyhydroxylated benzophenone

In some case, enzymatic oxidation,[60] using Horse Radish Peroxidase Laccase or even microorganism as *R. Buffonii*,[55] has been used as well. In the case of silver salts,[62] Fuse et al. suggested a radical mechanism for the formation of 1,7-di-hydroxyxanthone **69**. In the proposition, a single electron transfer (SET) to form xanthone ring **67** occurs, generating a radical intermediate stabilised by the 3-hydroxyl group. This is followed by a second SET, resulting in the re-aroma-tisation reaction forming xanthone core **69** (Scheme 17).



Scheme 17 Proposed radical mechanism for the formation of 1,7-di-hydroxyxanthone[62]

Recently, Suzuki et al.[63] developed the total synthesis of Atroviridin using MnO_2 as oxidant to form the xanthone core. In their case, the proposed mechanism relies on the formation of *p*-quinone **71** followed by a 1,4-addition of the free hydroxyl group leading to keto-tautomer intermediates **72** and **73**, which are demethylated to yield Atroviridin (Scheme 18).

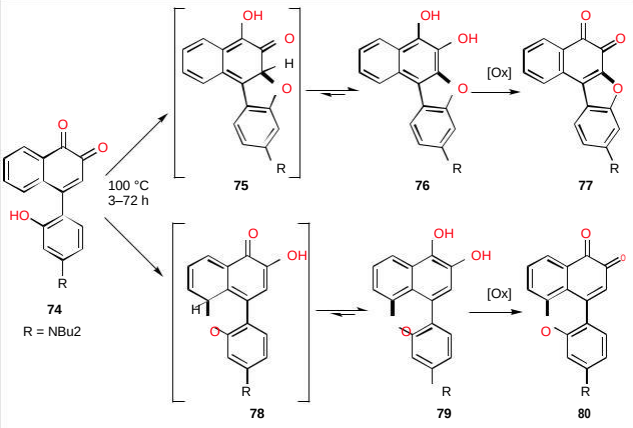


Scheme 18 Proposed mechanism for the formation of Atroviridin[63]

3.4 Miscellaneous

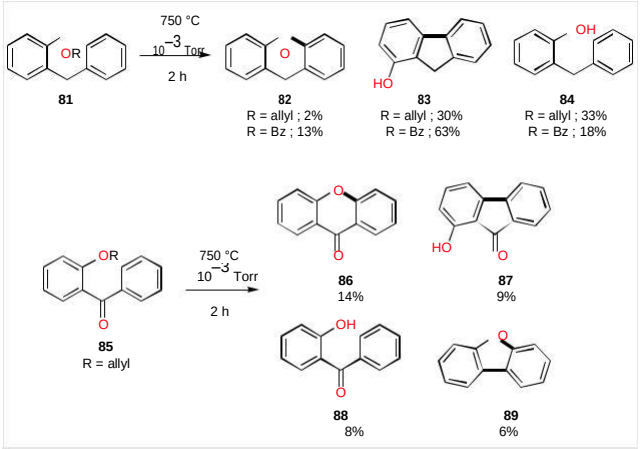
3.4.1 Conjugated Addition on Quinone

In 2006, Yoshida reported a synthesis of furanyl and pyranyl derivatives based on the conjugated Cu- and Ni-promoted addition of a hydroxyl group on the adjacent *ortho*-quinone moiety (Scheme 19).[64]



Scheme 19 Synthesis of furan and pyran derivatives through quinone intermediates[64]

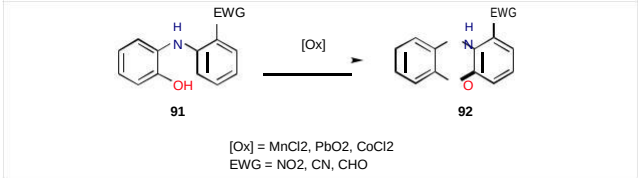
During the study of the reaction, they observed that $Cu(OAc)_2$ was the most effective oxidiser, and that the sol-vent polarity has a strong effect on the regioselective out-come of the cyclisation. For instance, in the case of DMSO, six-membered ring was preferentially obtained (ratio of 4.4:1), whereas in $MeNO_2$ only the five-membered ring was formed. Another method for preparing cyclic diaryl ethers is based on Flash Vacuum Pyrolysis (FVP). The idea of this approach is to generate hydroxyl radical species that under-go an intramolecular cyclisation reaction. However, these reactions are usually low yielding and lack regioselectivity. In their early report, Cardogan and McNab described the cy-clisation of 2-(allyloxy) or 2-(benzyloxy)diphenylmethane **81** to produce xanthene **82**, fluorene **83**, and phenol **84** de-rivative. In the case of 2-(allyloxy)benzophenone **85**, they were able to obtain a mixture of xanthone **86**, fluorenone **87**, methylbenzylphenol **88**, and dibenzofuran **89** (Scheme 20).[65]



Scheme 20 C–O bond formation by Flash Vacuum Pyrolysis[65]

3.4.2 Phenoxazine

Phenoxazines (POZs) are natural organic dyes that can be used in applications such as hole-transporting materials, bio-imaging, dye-sensitised solar cells (DSSCs), and lasers.[66] POZs **92** is usually obtained by oxidative cyclisation of 2-(phenylamino)phenol **91** in the presence $MnCl_2$[67] PbO_2 [68] or $CoCl_2$.[69] Substrates bearing EWGs (e.g., nitro, cyano, and acetyl groups) revealed to be compatible with the oxidative reaction conditions (Scheme 21).

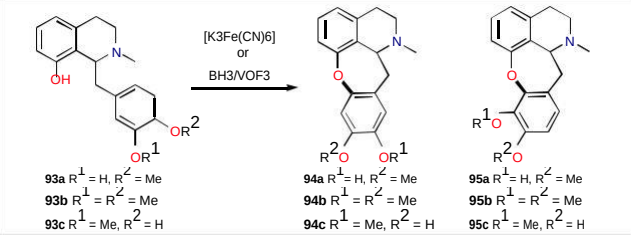


Scheme 21 Phenoxazine formation

4 Seven-Membered Rings: Cularines

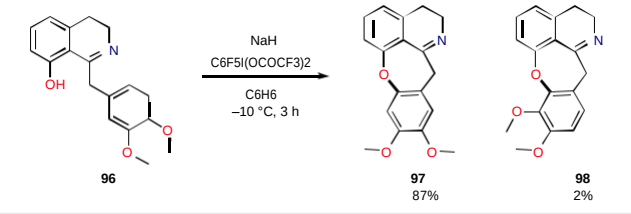
The most common C–H bond cleavage/C–O bond formation developed so far for engineering O-annulated seven-membered rings is that used for the synthesis of cularines. In 1974, Jackson et al. reported an oxidative intramolecular coupling of tetrahydrobenzylisoquinoline derivatives **93a** in the presence of $K_3[Fe(CN)_6]$ to produce cularine **94a** and isocularine **95a** in 2.5%, and 5% yield, respectively.[70] The

method was improved by using an N-borane complex of **93b**, treating it with VOF_3 to yield **94b** in 56% yield (Scheme 22).[71]

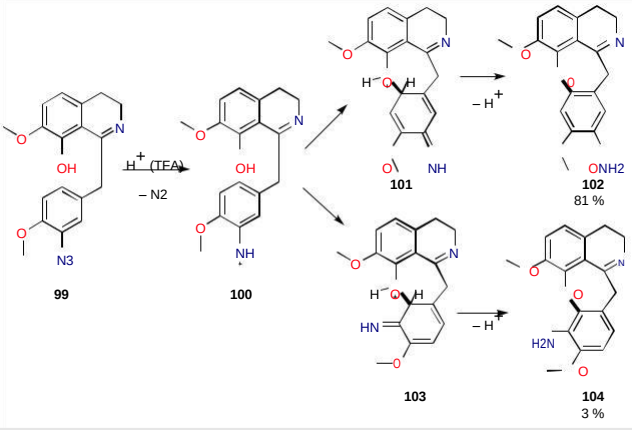


Scheme 22 Synthesis of cularines and isocularines with $K_3[Fe(CN)_6]$[70] and VOF_3[71]

Instead, the synthesis of didehydronorcularine **97** was achieved by Rodrigues and Abramovitch using $C_6F_5I(OCOCF_3)_2$, yielding the desired cyclic diaryl ether in 87%, together with traces of *ortho*-cyclised derivative **98** (Scheme 23).[72] The same team also reported the synthesis of cularines through the use of nitrenium ions (Scheme 24), generated in situ by acid-catalysed decomposition of the azide precursor **99**. 1,4-Type intramolecular addition of the *peri*-hydroxyl group, followed by tautomerisation of the imine intermediate, yielded amino-didehydronorcularine **102** (81%) as the major product.[72] Notably, the intramolecu-lar addition reaction occurs at the least sterically hindered site, namely in *para*-position with respect to the amino functionality.



Scheme 23 Didehydronorcularine formation[72]



Scheme 24 Synthesis of aminocularines by the nitrenium ion route[72]

5 Conclusion

In conclusion, in this review we have described the cur-rent synthetic approaches to prepare cyclic diaryl ethers through C–H bond cleavage/C–O bond formation. Our at-tention were focused on five- (furano), six- (pyrano), and seven-membered rings. In the case of the formation of fura-no-type rings, it is apparent that the C–O bond formation mediated by Pd and Cu salts is generally triggered by the activation of the C–H bond. High yields are usually obtained with metal-catalysed protocols if compared to classical oxi-dative or light-driven approaches. As far as the pyrano rings are concerned, no clear mechanisms have been postulated so far, and the reaction protocol greatly varies depending on the type of the six-membered diaryl ether, namely, dibenzoxanthene (DBX), *peri*-xanthenoxanthene (PXX), xanthones, and phenoxazine (POZ). At last, seven-mem-bered diaryl ethers are rare, and only methods to prepare cularines have been discussed.

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