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REVIEW

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Recent advances in the synthesis of xanthones and azaxanthones

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Xanthones are important *O*-heteroaromatic tricyclic molecules exhibiting a wide range of bioactivities and can represent a showcase to highlight the recent techniques and strategies in organic synthesis towards lead discovery and optimization. This review gives an insight into the recent literature disclosed to obtain the xanthone core, including the drug-like azaxanthones, isosteres of xanthones, by exploiting the optimization of well-known procedures as well as disruptive developed methodologies. With this review, it is expected to provide a useful chemical toolbox to synthetic medicinal chemistry focusing on these privileged structures, covering from 2012 to 2020, with some older examples of azaxanthones.

1 Introduction

Over the past few decades, strategic advances have been made in medicinal chemistry and organic synthesis that accelerated drug discovery. Diversity-oriented synthesis, photo-induced reactions, biorthogonal chemistry with new and eco-friendly reagents, late-stage diversification, and artificial intelligence are among the approaches involved in some of the recent breakthroughs in drug discovery.[1,2] More than 85% of all biologically-active chemical entities contain a heterocycle which provides a useful tool for lead optimization.[3,4] This current review aims to emphasize a particular class of heterocycles, xanthones; the use of these advances allow one to speed up their synthesis and lead optimization process.

Xanthones are naturally occurring compounds that can be found as secondary metabolites in diverse terrestrial and marine plants, fungi, and lichen.[5–8] Chemically, xanthones (9*H*-xanthen-9-ones) comprise a family of compounds with an oxygen-containing dibenzo-γ-pyrone heterocyclic scaffold (Fig. 1).[9,10] As a privileged structure, this family of compounds is able to provide a wide range of different substitutions modulating several biological responses, thus being considered a promising and interesting structure for drug development.[11,12] Azaxanthones (Fig. 1) are molecules with one or more nitrogen atoms placed in the aromatic moiety of the xanthone chromophore. N-Heterocycles, present in both natural products and synthetic compounds, constitute important structural motifs in medicinal chemistry, capable of showing a plethora of biological activities.[13] This allied to the privileged O-heterocyclic xanthone scaffold, which can give rise to new molecules, gifted with interesting activities and drug-likeness, and ultimately to the discovery of new lead compounds.[14] Azaxanthones also have advantages over acridones, such as being better chromophores and presenting a higher solubility in water.[15] In terms of the structural diversity of N-heterocycles, azaxanthones can be classified into a six-membered ring group, if one of the rings is a pyridine or a pyrimidine, or into a five-membered ring group, if one of the rings is a pyrazole or a triazole (Fig. 1).

In the last decade, both natural and synthetic xanthones have been reported with diverse biological and pharmacological properties,[5,6,8,16] including antibacterial,[8,17–27] antifungal,[8,17,20,21,28–30] antiviral,[31] antioxidant,[32–37] antiobesity,[38] anti-inflammatory,[5,17,39–41] anticoagulant,[42] and antitumour.[36,43–58] Particularly, some xanthones' molecular targets have been disclosed, including clinically important enzymes such as α-glucosidase,[59–63] topoisomerase,[64,65] *p*-glycoprotein,[66–68] and acetylcholinesterase[33,69,70] and also protein–protein interactions, such as p53-MDM2.[71–74] Similarly, a variety of biological activities was also disclosed for azaxanthones, depending on the side chains which can be found in their scaffolds. The activities described include antitumour,[75,76] anti-allergic, bronchodilator, anti-inflammatory, and analeptic.[77,78] In fact, one azaxanthone, amlexanox, was approved by the Food and Drug Administration (FDA) in 1996, as an antiallergic and anti-inflammatory immunomodulator, used for the treatment of aphthous ulcers.[79] Although its mechanism of action is not fully understood, it is thought to inhibit the release of histamine and leukotrienes from white

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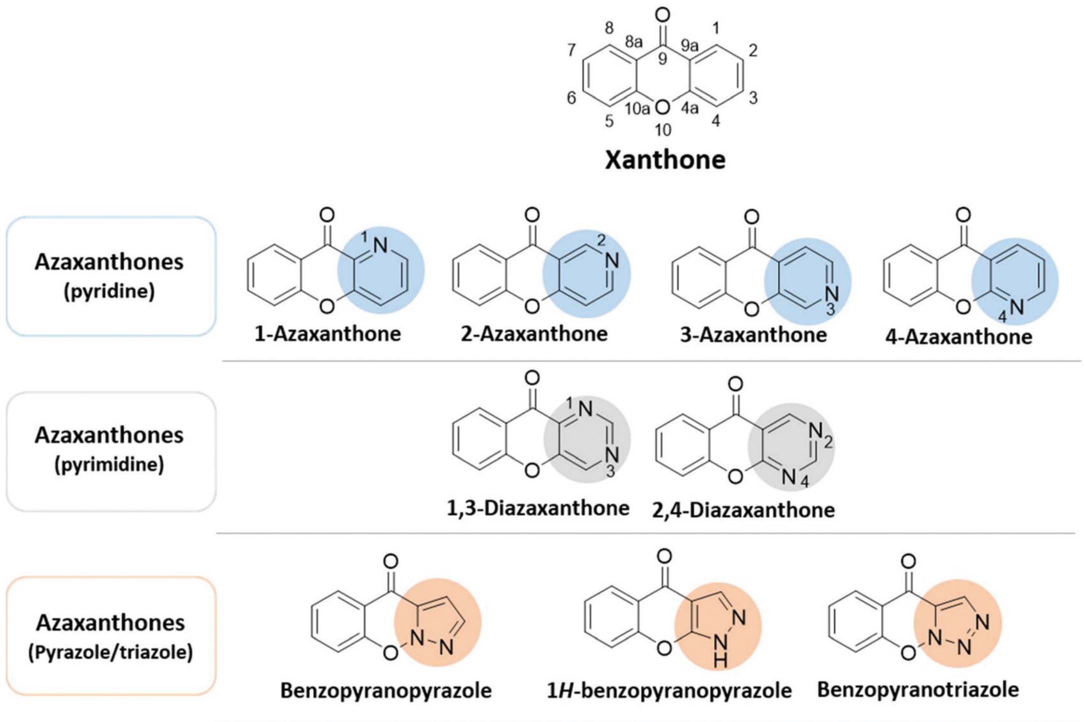


Fig. 1 Xanthone and azaxanthone scaffolds.

blood cells.[80] Additionally, amlexanox and derivatives have shown potential as antitumour agents, particularly in tumour cells expressing one or more proteins of the S100 family, which include breast, colon, lung, pancreas, skin, oesophagus, bladder, and other tumours.

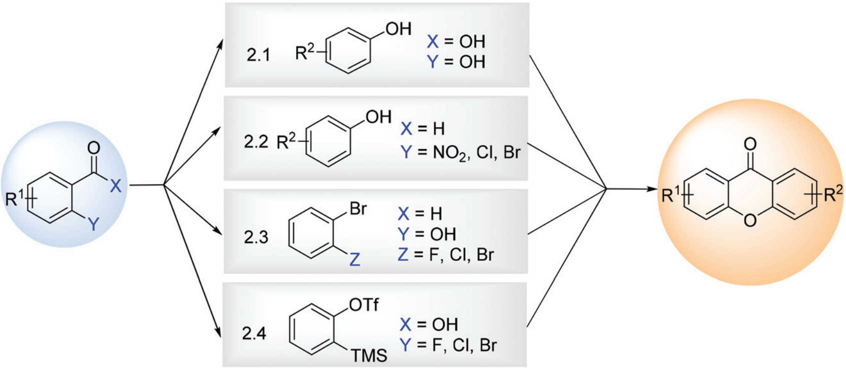
The first methods for the synthesis of xanthones were introduced by Michael and Kostanecki in 1883–1891[81,82] and in the 20th century and until 2012 several extensive reviews have reported the state of the art regarding the synthesis of xanthones.[9,10,83,84] More recently reviews have focused on the synthesis of a very specific class of derivatives like carboxyxanthones,[85] hydroxanthones,[86] arylxanthones,[87] and thioxanthones[88] and, although azaxanthones have demonstrated therapeutic potential and interest as sensitizing chromophores,[89–94] their reports in medicinal chemistry are still sparse in the literature. Therefore, in this review, the recent exploitation of both scaffolds was considered from a medicinal chemistry point of view, with advanced synthetic methodologies applied for obtaining bioactive derivatives being displayed in the sections below.

2 Synthesis of xanthones in one reaction step *via* condensation of two aryl building blocks

Methods for the synthesis of xanthones relying on a one-step methodology from readily available building blocks are still quite popular due to their simplicity and possibility of diverse substitution patterns. Four distinct approaches were developed and optimized over the last few years (DCXZ Scheme 1), involving the classical condensation of a salicylic acid with a phenol derivative (section 2.1), or involving an aryl aldehyde with a phenol derivative (section 2.2), a salicylaldehyde with 1,2-dihaloarenes (section 2.3), or an *o*-haloarenecarboxylic acid with arynes (section 2.4).

2.1 Synthesis of xanthones by condensation of a salicylic acid with a phenol derivative

The classical Grover, Shah and Shah method[95,96] constitutes a suitable approach for the synthesis of hydroxyxanthones from easily available salicylic acid derivatives and phenols heated along with zinc chloride in phosphoryl chloride.[33,39,43,49,51,60,65,97–104] For the reaction to proceed directly to the desired xanthone, the 2,2′-dihydroxybenzophenone intermediate must contain an additional hydroxyl moiety *ortho* to the carbonyl group. Usually phloroglucinol is used in order to overcome this limitation; however, when other phenol derivatives like resorcinol are used, the synthetic pathway stops at the benzophenone form.[53,105] Consequently, an additional cyclization step is required towards the conversion into xanthones. These and other limitations over this one-pot strategy towards simple xanthones led to modifications and development of new synthetic methods.[9,10] Substitution of phosphorus oxychloride–zinc chloride by phosphorus pentoxide–methanesulfonic acid (Eaton's reagent) as an acylation catalyst generally led to better results.[18,19,23,24,33,35,40,50,54,59,63,70,106–121] Since both



Scheme 1 Methodologies for the synthesis of xanthones in one reaction step *via* condensation of two aryl building blocks.

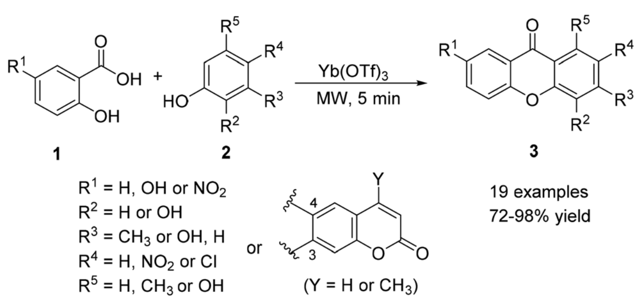
of these methodologies had previously been extensively reviewed,[9,10] they will not be discussed herein.

Rare earth metal triflates were used as unique Lewis acids to promote xanthone synthesis catalysed by $Yb(OTf)_3$ hydrate from 2-substituted benzoic acids and differently substituted phenols under microwave irradiation (Scheme 2).[122]

Other metal triflates from the lanthanide series (*e.g.* lanthanum, europium, and gadolinium) led to the poorest yields, which can be explained by the fact that Yb^{3+} is the 'hardest' cation and thus the most oxophilic, due to its smaller ionic radius.[122] Mechanistically, an initial Friedel–Crafts acylation can be considered towards the formation of a benzophenone intermediate, with further ring closure by displacement of the OH group coordinating the metal centre by the OH on the adjacent ring. Combination of salicylic, gentistic or 5-nitrosalicylic acids with *m*-cresol, orcinol, phloroglucinol, resorcinol, pyrogallol, *p*-nitrophenol, *p*-chlorophenol, 7-hydroxycoumarin or 4-methyl-7-hydroxycoumarin led to the corresponding xanthones **3** in high yields (19 examples, 72–98%).[122]

2.2 Synthesis of xanthones by condensation of an aryl aldehyde with a phenol derivative

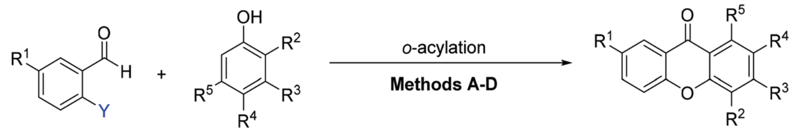
Highly selective and efficient transition metals like copper and iron catalytic systems have been recently employed for the synthesis of xanthones due to the associated concept of eco-friendliness, considering atom economy, low toxicity and atom



Scheme 2 Synthesis of xanthones *via* a microwave assisted reaction catalysed by $Yb(OTf)_3$.

efficiency.[123–126] In the scope of a study on the *o*-acylation of phenols with various aryl aldehydes using $CuCl_2$ as the catalyst in the presence of triphenylphosphine, it was found that benzophenones were obtained when benzaldehyde or 3- or 4-substituted aryl aldehydes were employed. Nevertheless, when 2-substituted aryl aldehydes reacted with phenols, xanthones were obtained (Table 1, Method A), first *via ortho*-acylation of phenols with 2-substituted aryl aldehydes with further ring closure under basic conditions, with *orto*-substituents of the aryl aldehydes serving as leaving groups (LG).[123] The scope of the reaction of 2-nitrobenzaldehydes and phenols was investigated after an initial screening of leaving groups, showing that electron-donating groups (EDG) (alkoxy, alkyl, aryl, and halides) were well tolerated on phenols, promoting the reaction. On the other hand, electron-withdrawing groups (EWG) (NO_2 or CN) block the reaction completely, the main drawback of this methodology.[123] Although these results are promising for eco-friendly reasons, they still employ ligands and expensive catalysts which are not recycled. To surpass these disadvantages, Menendéz *et al.*[124] optimized the reaction conditions using a magnetic nanocatalyst consisting of CuNPs (NP = nanoparticles) on silica coated maghemite to catalyze the reaction between *ortho*-substituted benzaldehydes and phenols (Table 1, Method B). Provided with a high surface area, nanocatalysts were used to afford a more significant advancement in catalytic activity over conventional catalytic methods. This synthetic protocol was compatible with the presence of a variety of functional groups in the starting phenolic building blocks, affording the desired xanthones in good to excellent yields, with recovery of the catalyst.[124] Ramani[125] used Fe_3O_4 nanoparticles under ligand-free conditions to catalyze *o*-benzoylation of phenols with aryl aldehydes for the synthesis of xanthones, with lower yields than the reported for the latter two methodologies (Table 1, Method C). Later, Venkanna[126] used magnetically separable nano-$CuFe_2O_4$ to catalyze *o*-acylation (Table 1, Method D). Xanthone derivatives were generally obtained in good yields from the condensation of diverse phenols with 2-nitrobenzaldehydes using nano-$CuFe_2O_4$ as the catalyst, K_3PO_4 and DMF at 80 °C, in an open flask, for 10 h. Comparing the four methodologies (Table 1), and looking at

Table 1 Synthesis of xanthones *via* a one-step o-acylation of phenols with 2-substituted aldehydes



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Method A, Y = NO_2, OCH_3 or Br
$CuCl_2$, PPh_3, K_3PO_4, toluene, 110 ºC, air, 24 h

Method B, Y = NO_2
CuNPs, K_3PO_4. toluene, Ar, 2 h

Method C, Y = NO_2, Cl, Br
Fe_3O_4 NPs, K_2CO_3, toluene, 110 ºC, air, 24h

Method D, Y = NO_2
nano-$CuFe_2O_4$, K_3PO_4, DMF, 80 ºC, air

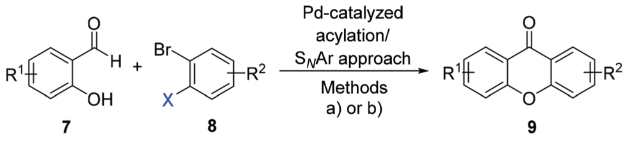
							% Yield/Ref.			
Entry	Y	R[1]	R[2]	R[3]	R[4]	R[5]	Method A[123 a]	Method B[124 a]	Method C[125 b]	Method D[126 b]
1	NO_2	H	H	H	OCH_3	H	87 (74)	98 (89)	—	—
2	NO_2	H	H	H	iPr	H	92 (81)	—	—	—
3	NO_2	H	H	H	H	H	81 (70)	84 (76)	65	89
4	NO_2	H	H	H	I	H	77 (62)	—	—	80
5	NO_2	H	I	H	H	H	73 (62)	—	—	78
6	NO_2	H	H	H	Br	H	72 (59)	78 (70)	—	86
7	NO_2	H	H	H	Cl	H	82 (73)	—	—	82
8	NO_2	H	Cl	H	H	H	76 (60)	—	—	74
9	NO_2	H	H	F	H	H	70 (58)	—	—	—
10	NO_2	H	H	H	F	H	71 (55)	—	—	79
11	NO_2	H	Ph	H	H	H	69 (55)	—	—	—
12	NO_2	H	C_4H_4		H	H	43 (30)	85 (77)	60	79
13	NO_2	H	Cl	H	Cl	H	75 (64)	—	—	—
14	NO_2	H	H	CH_3	CH_3	H	84 (72)	—	—	80
15	NO_2	H	CH_3	H	CH_3	H	90 (80)	—	—	—
16	NO_2	H	H	CH_3	CH_3	CH_3	73 (61)	—	—	—
17	NO_2	OCH_3	H	H	OCH_3	H	83 (70)	85 (72)	—	—
18	NO_2	OCH_3	H	H	iPr	H	82 (70)	—	—	—
19	NO_2	OCH_3	H	H	Cl	H	80 (69)	—	—	—
20	NO_2	OCH_3	Cl	H	Cl	H	68 (57)	—	—	—
21	NO_2	H	H	OCH_3	H	H	—	97 (86)	—	—
22	NO_2	H	OCH_3	H	H	H	—	91 (84)	—	—
23	NO_2	H	H	H	NO_2	H	—	60 (51)	—	—
24	NO_2	H	H	H	CF_3	H	—	63 (54)	—	—
25	NO_2	H	CH_3	H	H	H	—	89 (80)	—	76
26	NO_2	H	H	OH	H	H	—	75 (68)	—	—
27	Cl	H	H	H	H	H	—	—	55	—
28	Br	H	H	H	H	H	—	—	50	—
29	NO_2	H	H	H	*t*Bu	H	—	—	72	84
30	Br	H	H	H	*t*Bu	H	—	—	55	—
31	NO_2	H	H	CH_3	H	H	—	—	—	92
32	NO_2	H	H	H	CH_3	H	—	—	—	85
33	NO_2	H	H	C_4H_4		H	—	—	—	80
34	NO_2	CH_3[c]	H	H	H	H	—	—	—	78
35	NO_2	Br	H	H	H	H	—	—	—	75
36	NO_2	Cl	H	H	H	H	—	—	—	70

[a] ^{1}H NMR yield (isolated yield). [b] Isolated yields. [c] 4-Methyl-2-nitrobenzaldehyde.

the characteristics of eco-friendliness, reaction conditions and yields, methods B and D seem to be more suitable for the synthesis of xanthones from 2-nitrobenzaldehydes and phenols, with a good tolerance for different substituent groups on the phenol moiety.

2.3 Synthesis of xanthones by condensation of a salicylaldehyde and 1,2-dihaloarenes

Aside the *o*-acylation of phenols with 2-substituted aldehydes, the xanthone core can also be constructed through a selective palladium-catalysed acylation/nucleophilic aromatic substitution (S_NAr) approach of salicylaldehyde derivatives with aryl halides (Scheme 3).[127,128] The first methodology reported consisted of the use of a bulky electron-rich trialkylphosphine ligand, *n*-BuPAd$_2$, which prevents the decomposition of the palladium catalyst, observed with the use of other ligands.[128] The scope of the reaction was extended to 22 different xanthones (41–81% yield); however, only activated salicylaldehydes were tolerated, long reaction times (12 h) were needed, and it was impractical to recover and reuse the catalyst. A rapid and con-



a), X = F
R^1 = H, OCH_3, Cl, NO_2, or CO_2CH_3; R^2 = H, CH_3, Cl, F
$Pd_2(OAc)_2$, $BuPAd_2$, K_2CO_3, DMF, Ar, 120 °C, 12 h
(22 examples, 41-81%)

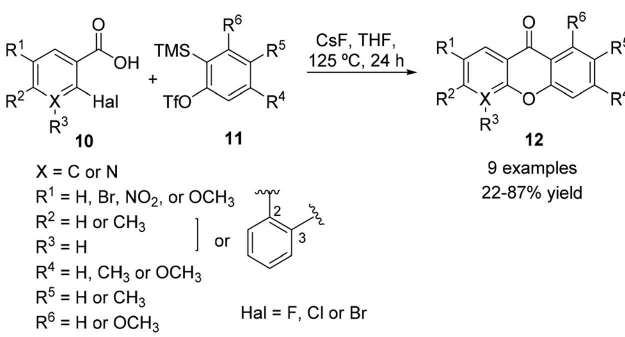
b), X = Br, Cl
R^1 = OH, CH_3, OCH_3, Br, Cl, NO_2, NEt_2, or C_4H_4; R^2 = CH_3, OCH_3, Br or NO_2
PdNPs/BC, K_2CO_3, DMF, MW, 250 W, 150 °C, 30 min
(20 examples, 54-88%)

Scheme 3 Synthesis of xanthones *via* the palladium-catalysed acylation/S_NAr approach.

venient ligand-free alternative was later reported for this direct annulation using a recoverable palladium nanocatalyst supported on a green biochar under microwave irradiation, with a drastic reduction in reaction times.[127] This eco-friendly strategy proceeded in very good yields (54–88%) and with high regioselectivity for a scope of 20 xanthone derivatives.

2.4 Synthesis of xanthones by condensation of *o*-haloarenecarboxylic acids with arynes

Dubrovskiy and Larock[129] reported the synthesis of xanthones *via* an intermolecular C–O addition of *o*-halobenzoic acids **10** to arynes **11** employing CsF and THF at 125 °C for 24 h.



Scheme 4 Synthesis of xanthones *via* an intermolecular C–O addition of *o*-halobenzoic acids to arynes.

Although *o*-chloro and *o*-iodo benzoic acids provided poor yields, *o*-fluorobenzoic acid afforded the desired xanthones **12** in good yields (Scheme 4). Diversification of substituents either in the benzoic acid building block or in the aryne moiety was well tolerated, and nine different xanthone derivatives were obtained, including an azaxanthone.

3 Synthesis of (aza)xanthones *via* the benzophenone route

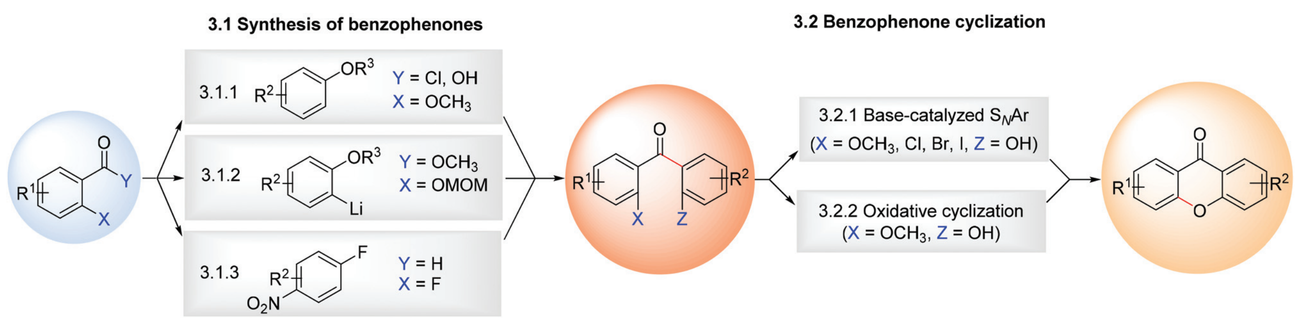
The limitations of some of the earlier one-step methodologies (*e.g.* Grover, Shah and Shah, section 2.1) led to the development of several multi-step approaches. The synthesis of xanthones *via* the benzophenone route is one of the most used approaches in which the benzophenone derivatives are easily accessed through (poly)oxygenated aromatic compounds with a benzoic acid derivative (section 3.1.1), followed by the cyclization of the benzophenone (section 3.1.2) into the xanthone scaffold (Scheme 5), usually achieved by base-catalysed intramolecular nucleophilic aromatic substitution. Considering the high versatility of this route, examples of the total synthesis of natural products using this strategy in the last decade[130–136] are presented in Fig. 2.

3.1 Synthesis of xanthones

3.1.1 Synthesis of benzophenones. The Friedel–Crafts acylation continues to be the method of choice for the synthesis of the benzophenone moiety, when xanthones are obtained *via* a benzophenone route (section 3.1.1.1).[28,47,66,71,137–140] Additional approaches for the synthesis of the benzophenone moiety include the halogen–lithium exchange (section 3.1.1.2) and NHC-catalysed aroylation (section 3.1.1.3) (Scheme 6).

Other methodologies were reported for the synthesis of benzephenones *via* an *o*-acylation of phenols using copper[123] and iron-mediated[125] approaches, or *via* a reductive decarbonylative coupling.[141] However, further investigations led to the attainment of the corresponding xanthone in one step and, therefore, they are addressed in the appropriate sections (section 2.2 and section 7.1).

3.1.1.1 Synthesis of benzophenones via Friedel–Crafts acylation of (poly)oxygenated aromatic compounds with a benzoic acid



Scheme 5 Strategies for the synthesis of xanthones *via* benzophenone.

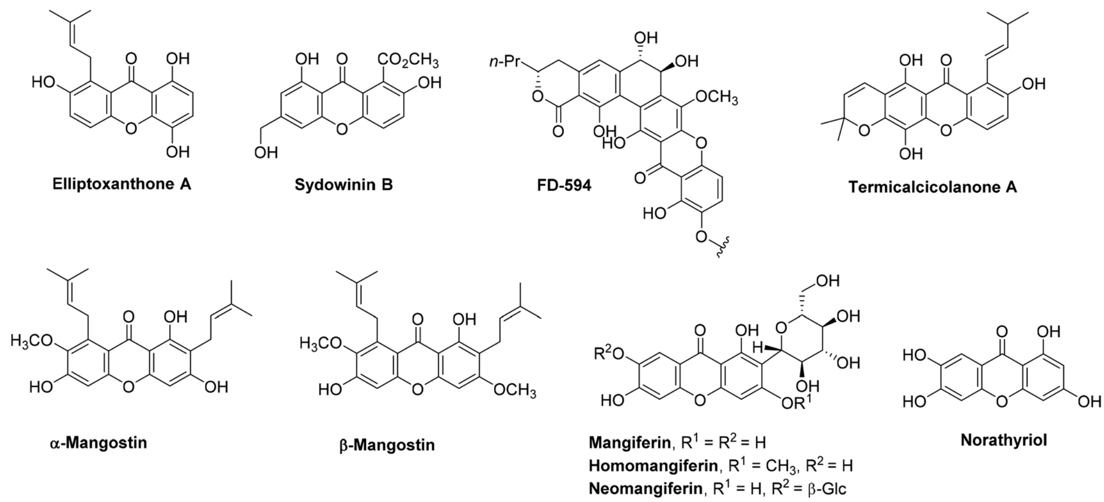
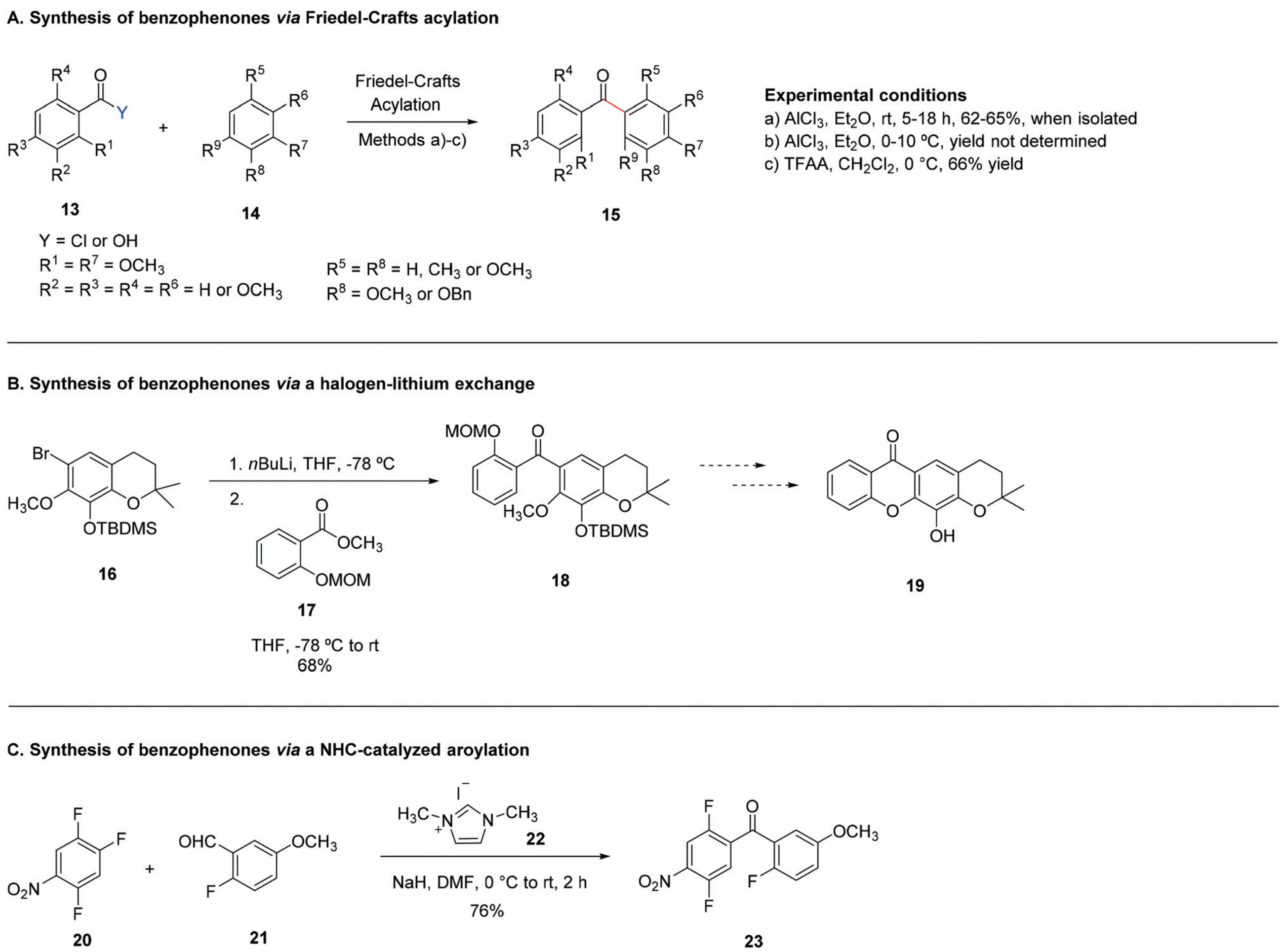


Fig. 2 Recent examples of the total synthesis of natural products using the benzophenone route.



Scheme 6 Synthesis of benzophenones.

derivative. Over the last few years, several examples of the synthesis of benzophenones *via* Friedel–Crafts acylation have been reported, mainly *via* classical reaction conditions employing an acid chloride and $AlCl_3$ as a Lewis acid catalyst (Scheme 6A).[28,47,66,71,137–139] When two methoxy groups are present in both R^1 and R^9 three different benzophenone derivatives can be formed: a benzophenone methoxylated at R^1 and R^9, and two benzophenone derivatives which result from the demethylation of the methoxy group in R^1 or R^9 (position *peri*-carbonyl). Hence, to avoid losses, usually the benzophenone derivatives are not isolated and the reaction crude is used directly towards cyclization to xanthones.[28,66,71,138] Other interesting strategies have been developed in the last few years for the synthesis of benzophenones, worth highlighting being the one in which the carbonyl bridge is introduced *via* a mild Friedel–Crafts reaction using trifluoroacetic anhydride (TFAA) (Scheme 6A).[140] This methodology was developed in the scope of a study to find novel PGAM1 inhibitors and involves the *in situ* formation of a mixed anhydride that results from the reaction of the benzoic acid derivative with TFAA, in order to make the carbonyl adjacent to the aromatic ring more susceptible to nucleophilic attack.[140] Due to the limitations in the tolerated substituents that can be present at either the benzoic acid derivative or the (poly)oxygenated aromatic compound in order for cyclization to occur, this methodology is usually employed as the starting point for the synthesis of more complex xanthone derivatives.

3.1.1.2 Synthesis of benzophenones via a halogen–lithium exchange. The halogen–lithium exchange benzophenone cyclization is not used as commonly as the Friedel–Crafts acylation, but can still be considered a valuable tool for the synthesis of benzophenone derivatives. Studies on the synthesis of 12-hydroxy-2,2-dimethyl-3,4-dihydropyran[3,2*b*]xanthene-6(2*H*)-one (**19**), a p53-MDM2 inhibitor,[74] led to benzophenone **18**, obtained from halogen–lithium exchange of the previously synthesized benzopyran **16** and *O*-protected MOM (methoxymethyl) benzyl salicylate **17** (Scheme 6B).[46]

3.1.1.3 Synthesis of benzophenones via a NHC-catalysed aroylation. N-Heterocyclic carbenes (NHC) can be employed both as ligands for transition-metal systems or as small-molecule organocatalysts for chemical synthesis. In a nucleophilic aroylation catalysed by NHC **22**, the 4-fluoro group of trifluoronitrobenzene (**20**) is replaced by the aroyl group originating from aldehyde **21** to afford the corresponding benzophenone **23** (Scheme 6C).[133] This versatile methodology was applied in the total synthesis of termicalcicolanone A (Fig. 2), an anticancer natural xanthone.[133]

3.1.2 Benzophenone cyclization. The base-catalysed intramolecular nucleophilic aromatic substitution is undoubtedly the most frequently used strategy for the cyclization of benzophenones to xanthones (section 3.1.2.1). This methodology involves the presence of a hydroxyl group in position 2 and a functional group, normally a methoxy, which can behave as a leaving group in position 2′ of the benzophenone, usually in the form of methanol. Other methodologies include oxidative cyclization (section 3.1.2.2) with new and greener reaction conditions being reported in the last few years.

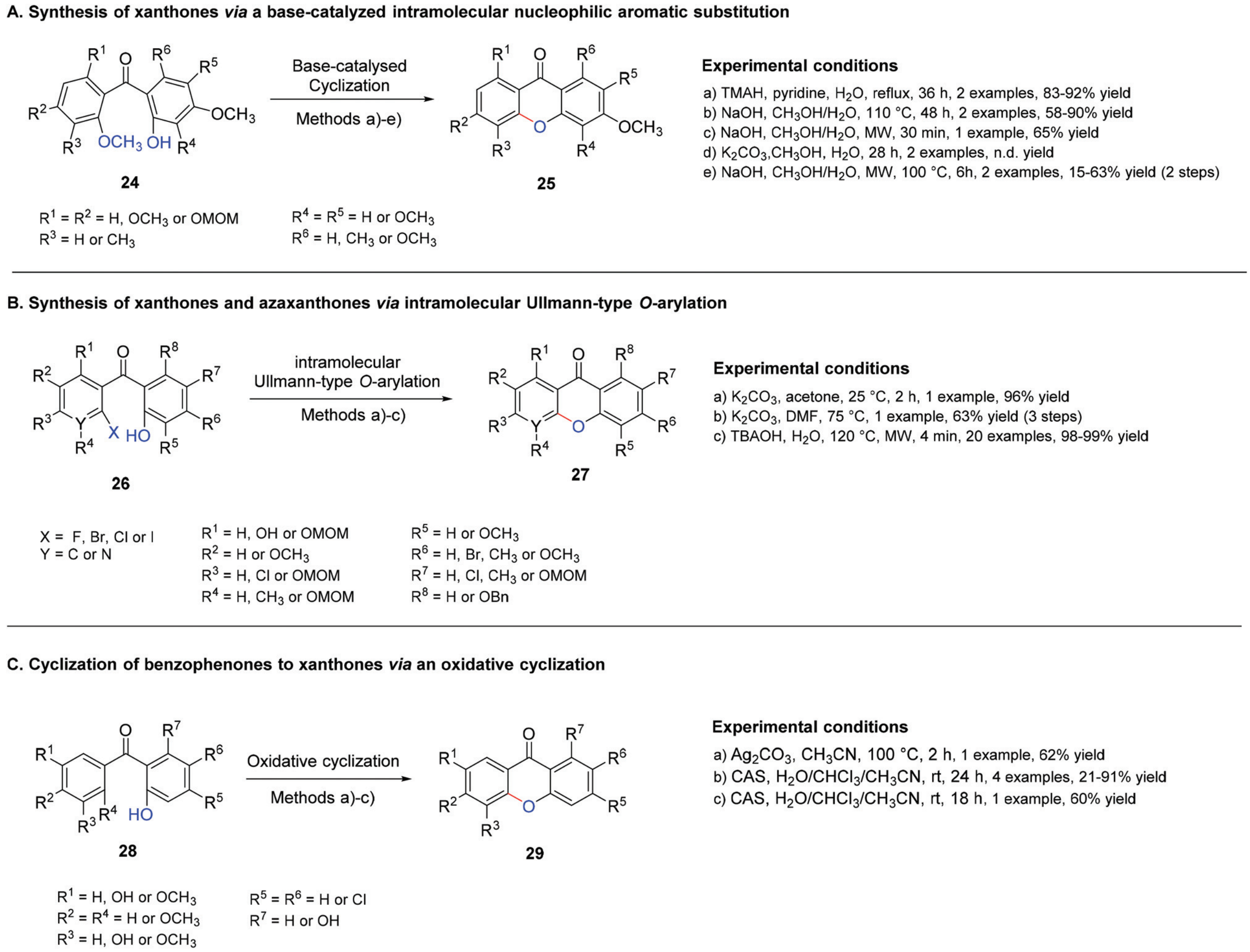
3.1.2.1 Cyclization of benzophenones to xanthones via a base-catalysed intramolecular nucleophilic aromatic substitution. Although the classical methodologies are widely used,[130,132,137–140] some improvements, especially in terms of yields and shorter reaction times, were achieved with microwave-assisted organic synthesis (MAOS).[28,46,47,66,71] Common bases used in this strategy are NaOH,[28,47,66,71,138] tetramethylammonium hydroxide (TMAH),[137,140] and K_2CO_3.[132,139] A greener approach was also reported using a combination of base/H_2O[142] (Scheme 7A).

In the presence of 2-halo-2′-hydroxybenzophenones, a transition-metal-free intramolecular Ullmann-type *O*-arylation reaction (Scheme 7B) can be employed for the synthesis of the corresponding xanthones **27**, either using K_2CO_3 or tetrabutylammonium hydroxide (TBAOH) as a base.[143] The latter is an efficient, rapid, and green method which uses microwave irradiation, resulting in a short reaction time and excellent yields. The *O*-arylation reaction proceeds smoothly, regardless of the nature of the halogen leaving group present in the aromatic moiety, with several functional groups being well-tolerated in all the examples, and extendable to the synthesis of azaxanthones. Although the desired xanthones **27** were produced in comparatively lower yields when in the presence of 1-hydroxynapthalene, in 4 min under MW irradiation, quantitative yields could be obtained when the reaction time was extended to 8 min. Azaxanthone was prepared in two minutes with an excellent yield (98%).[143]

3.1.2.2 Cyclization of benzophenones to xanthones via an oxidative cyclization. Despite not being used as often as the base-catalysed intramolecular nucleophilic aromatic substitution, methodologies based on the oxidative cyclization of the benzophenone are also employed for the synthesis of xanthone derivatives. Studies on the cyclization of the readily available model substrate 2,3′,5-trihydroxy benzophenone **28** revealed that the combination of Ag_2CO_3 and CH_3CN, at 100 °C for 2 h gave the best results towards the cyclization product, with the hydroxyl group being crucial for cyclization that occurs *via* a single-electron transfer mechanism[144] (Scheme 7C). To obtain 1,5,7-trisubstituted-3-pyridylxanthones with potential as insecticides, the target precursor 1,5,7-trihydroxy-3-chloroxanthone was cyclized using the optimized reaction conditions, in the route for the synthesis of several 1,5,7-trisubstituted-3-pyridylxanthones.[144] Ceric ammonium sulfate (CAS)[145,146] and ceric ammonium nitrate (CAN)[146]-mediated oxidative cyclization of benzophenones was also reported, although some limitations were observed with the formation of a xanthone-related dione. A possible mechanism for the formation of this secondary product was proposed with the formation of a radical cation with subsequent nucleophilic addition of the phenol, oxidation with CAN, and addition of water followed by elimination of methanol.[145]

3.2 Synthesis of azaxanthones

The synthesis of azaxanthones *via* the benzophenone route usually employs the preparation of the required benzophenone through Friedel–Crafts acylation (Scheme 8A), deprotocupration–aroylation (Scheme 8B), or even the formation of an intermediate alcohol *via* metal-mediated strategies, which is further oxidized to the corresponding ketone (Scheme 8C and D). Cyclization is typically achieved *via* S_NAr.

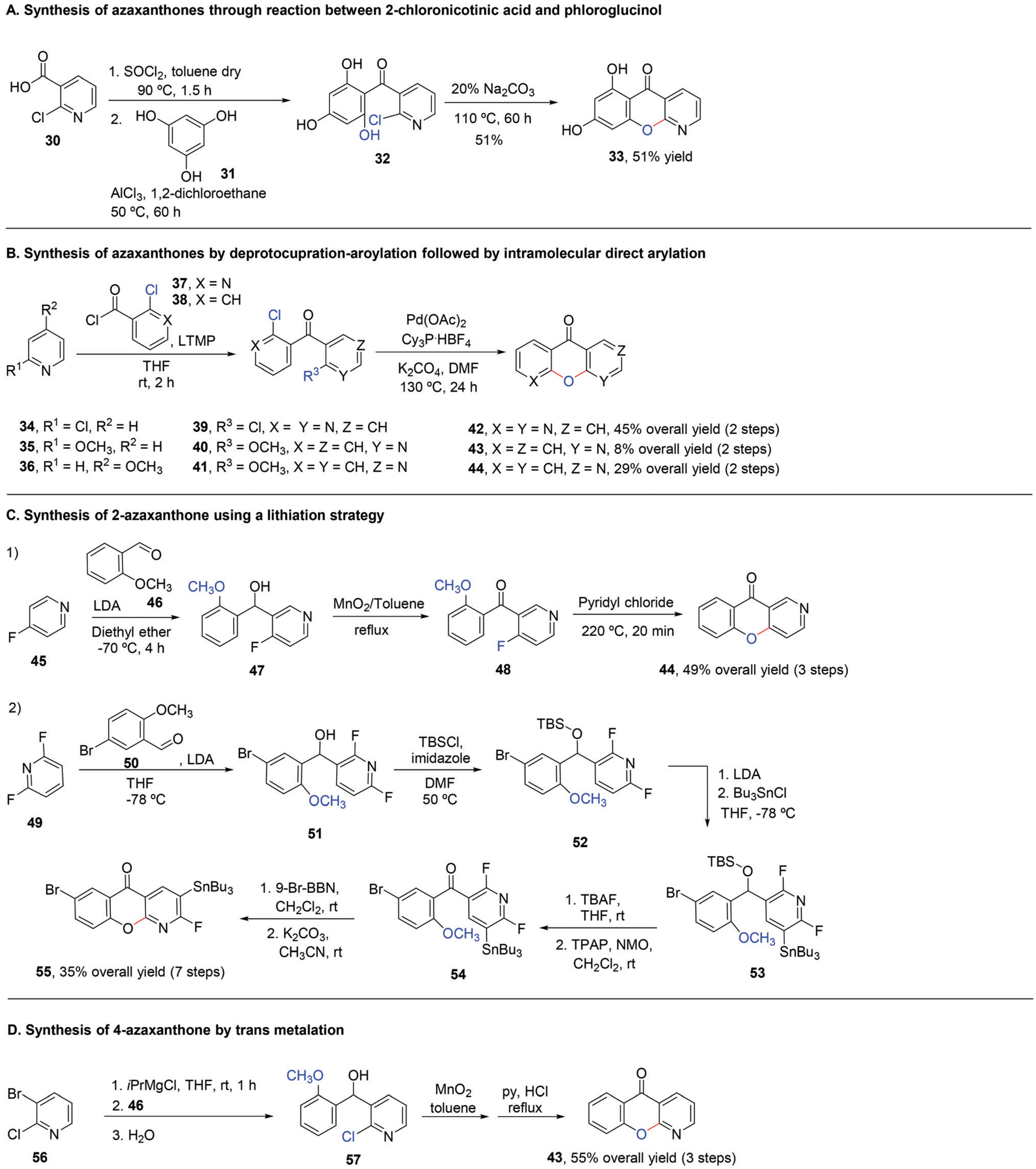


Scheme 7 Synthesis of xanthones *via* benzophenone cyclization.

3.2.1 Synthesis of azaxanthones through the reaction between 2-chloronicotinic acid and phloroglucinol. Kolokythas *et al.*[76] have studied the potential of pyranoxanthenones and pyranothioxanthenones, as potential cytotoxic agents closely related to the broad spectrum antitumour alkaloid acronycine (Scheme 8A). As an outcome of this work, the carbocyclic moiety was replaced by the pyridine heterocycle isostere in the xanthone chromophore. Similarly to the work of Villani *et al.*,[78] formation of the corresponding acyl chloride of 2-chloronicotinic acid (**30**) and further reaction with phloroglucinol **31** provided ketone **32** which was then cyclized to dihydroxyazaxanthone **33** in 51% yield.[76]

3.2.2 Synthesis of azaxanthones through deprotocupration–aroylation followed by intramolecular direct arylation. Lithiocuprates, prepared from copper(II) chloride and lithium 2,2,6,6-tetramethylpiperidide (LTMP), can be used as bases for the deprotonative metalation of aromatic compounds. By using palladium as a catalyst for ring closure, it is possible to obtain not only the expected azafluorenones, but also azaxanthones, through cyclization, in the presence of oxygen-containing substituents or reagents.[147] Synthesis of azaxanthones **42–44** was achieved by using this approach. 4,5-Diazaxanthone (**42**), was prepared from 2-chloropyridine (**34**) and LTMP, which was stirred for two hours at 0 °C in THF, before the addition of the corresponding aroyl chloride (Scheme 8B). The 4,5-diazaxanthone **42** was produced in 45% overall yield (2 steps) after treatment with palladium(II) acetate and triciclohexylphosphine tetrafluoroborate. The second azaxanthone, 4-azaxanthone (**43**), was synthesized similarly, starting from 2-methoxypyridine (**35**) and chlorobenzyl chloride in 8% overall yield (2 steps). The second step was slightly different, and although $Pd(OAc)_2$ was used as a catalyst, tri-*tert*-butylphosphonium tetrafluoroborate was also employed (Scheme 8B). 2-Azaxanthone (**44**) was obtained through the same method as 4,5-diazaxanthone (**42**), using 4-methoxypyridine (**36**) and chlorobenzyl chloride (Scheme 8B), yielding 29% of the desired compound (overall yield for 2 steps).[147]

3.2.3 Synthesis of azaxanthones through metalation–lithiation. Metalation of π-deficient heterocycles, such as pyridine, has proven to be a good strategy towards obtaining compounds that could serve as the starting materials for azaxanthones. This methodology can be a powerful functionalization



Scheme 8 Synthesis of azaxanthones *via* the benzophenone route.

approach, since electrophilic substitutions are frequently hard to achieve in such molecules. Based on the fact that halogens can induce *o*-lithiation of pyridine, Marsais *et al.*[148] explored this route and one of their experiments led to the synthesis of 2-azaxanthone (**44**). The metalation of the starting material, 4-fluoropyridine (**45**), was achieved with complete chemoselectivity using lithium diisopropylamide (LDA) and *o*-anisaldehyde (**46**). The formation of butylated side products when using butyllithium attested the advantages of using LDA as a lithiation agent. The fact that the product, (4-fluoro-3-pyridyl)-2-methoxyphenylmethanol (**47**), precipitated with diethyl ether also constituted an advantage, as higher metalation yields could be reached. Oxidation of **47** with manganese dioxide led to (4-fluoro-3-pyridyl)-2-methoxyphenylmethanone (**48**) which when heated with pyridinium chloride yielded 2-azaxanthone (**44**), in 49% overall yield, obtained over 3 steps (Scheme 8C1).[148] A similar approach was used for the synthesis of halo-azaxanthones, starting from 2,6-difluoropyridine (**49**) and 5-bromo-2-methoxybenzaldehyde (**50**). A *tert*-butyldimethyl silyl (TBS) ether protection of the formed hydroxyl moiety and installation of a Bu_3Sn group after the second fluorine-directed *o*-lithiation of the pyridine were used as key steps in the synthesis of trisubstituted azaxanthone **55** in 35% yield (overall yield considering 7 steps) (Scheme 8C2).[149]

3.2.4 Synthesis of azaxanthones through transmetalation. It is clear that metalation reactions are useful, with direct reactions with electrophiles or transmetalation, leading to cross-coupling reactions, being the most important. However, the lithiation reactions previously described require low temperatures, and, added to the fact that halogen–lithium exchange is extremely temperature-sensitive, that can be limiting, making them difficult to perform in an industrial setting.[150] Therefore, the search for alternative reactions led to the development of pyridylmagnesium reagents that could either take part in electrophilic trapping or coupling reactions. In this scope, the halogen–magnesium exchange methodology was preferred over the Grignard reaction, as the direct access by oxidative addition of magnesium to the halopyridine is challenging to accomplish, even with magnesium activation.[150] Studies on synthetic routes leading to new pyridine derivatives through bromine–magnesium exchange[148,150] revealed that isopropylmagnesium chloride (iPrMgCl) was the best exchange reagent, and THF was the best solvent. The fact that this reaction occurs at room temperature posed as an advantage. 4-Azaxanthone (**43**) was prepared starting from 3-bromo-2-chloropyridine (**56**) (Scheme 8D). Metalation with iPrMgCl, using THF as the solvent, at room temperature and further reaction with *o*-anisaldehyde (**46**) resulted in the formation of alcohol (**57**), which was then subject to oxidation and ring closure reactions affording **43** as described before, in 55% overall yield (3 steps).

4 Synthesis of (aza)xanthones *via* the diaryl ether route

The diaryl ether synthesis comprises the reaction between aryl halides and phenols which are further cyclized to the xanthone core. Like the benzophenone route, the diaryl ether route can then be divided into two steps: the synthesis of the diaryl ether (section 4.1.1) and the cyclization of the diaryl ether (section 4.1.2) (Scheme 9). This approach is particularly useful in the synthesis of 1,2-dioxygenated xanthones, when the pattern of substitution of the target xanthone cannot be obtained following the electrophilic aromatic substitution rules and/or is also dependent on the presence of bulky groups giving rise to isomeric mixtures. Nevertheless, due to generally higher yields obtained with intermolecular acylations when compared to the Ullmann ether syntheses, the recent examples of the total synthesis of natural products using the diaryl ether route are quite scarce, contrary to the existing ones *via* the benzophenone route (Fig. 3).

4.1 Synthesis of xanthones

4.1.1 Diaryl ether synthesis. With the extensive development of several methodologies towards xanthone synthesis, either through the benzophenone route (section 3) or even by

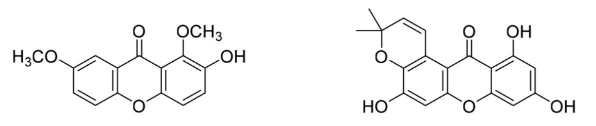
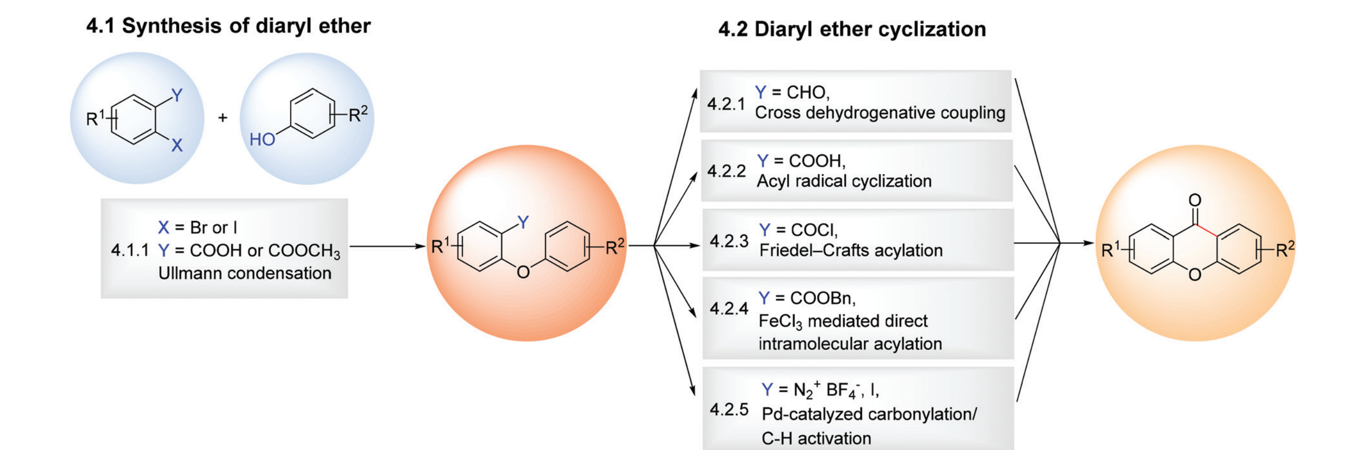


Fig. 3 Recent examples of the total synthesis of natural products using the diaryl ether route.



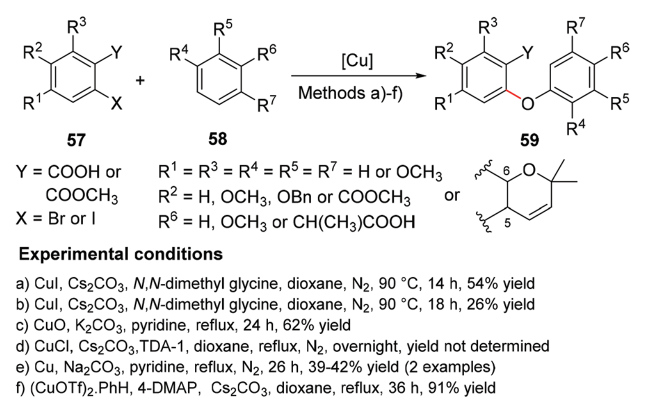
Scheme 9 Strategies for the synthesis of xanthones *via* diaryl ether.

one-step methodologies (section 2) or newer strategies (section 7), fewer examples involving other procedures have been described in recent times. When used, diaryl ether synthesis is usually achieved *via* the classic Ullmann condensation (section 4.1.1.1), which consists of the coupling of an aryl halide with a phenol (Scheme 9).

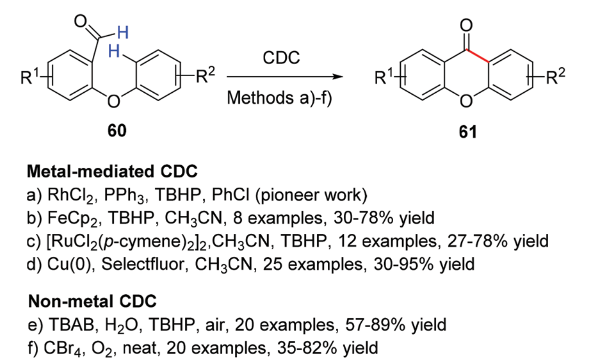
4.1.1.1 Synthesis of diaryl ether by coupling of an aryl halide with a phenol – Ullmann condensation. While some modifications of the coupling of an aryl halide with a phenol using Ullmann conditions have been described in the last few years, copper continues to be the metal of choice for this coupling. Common bases for Ullmann type reactions are K_2CO_3 and Cs_2CO_3 and some variations in the copper catalyst include the use of CuI,[45,151] CuO,[152] CuCl[153] or Cu/Cu_2O.[154] Since this methodology has already been extensively reviewed, recent examples are summarized in Scheme 10 and will not be widely discussed. However, it is worth mentioning a new copper-(I)-catalysed approach that, when compared to the classical Ullmann reaction protocols, requires only small amounts of copper catalyst and mild temperatures, with better overall yields, even when tested on a larger scale. The Buchwald's $Cu(OTf)_2$–benzene complex proved to be extremely effective against the classic CuI when combined with 4-dimethylaminopyridine (4-DMAP), to give the desired diaryl ether in high yields.[155] One of the synthesized xanthones showed typical xanthone fluorescence properties suitable for studying folding processes of polypeptides by triplet–triplet energy transfer (TTET).[155]

4.1.2 Cyclization of the diaryl ether. To be used as substrates in the synthesis of xanthones, diaryl ethers should contain certain molecular characteristics so that the next step, cyclization, can occur. Over the last few years, several approaches to the xanthone skeleton from a range of functionalized diaryl ethers *via* various mechanisms have been developed, depending largely on the functionality existing in the *ortho* position to the ether (Scheme 9, Y). When in the presence of an aldehyde derivative (Y = CHO), the most common methodology is *via* cross-dehydrogenative coupling (CDC, section 4.1.2.1). This strategy has received increasingly attention in recent years due to the fact that it does not require prefunctionalized coupling partners, can be extended to a wide scope of derivatives, and involves a few steps, and consequently high atom economy. In the presence of a carboxylic acid derivative (Y = COOH, COCl, COOBn), three approaches can be followed, depending on the nature of the derivative: an acyl radical cyclization *via* photoredox catalysis using methylene blue as a photosensitizer (section 4.1.2.2, Y = COOH), a metal-free variant of the intramolecular Friedel–Crafts acylation (section 4.1.2.3, Y = COCl), and a $FeCl_3$ mediated direct intramolecular acylation of esters (section 4.1.2.4, Y = COOBn). However, the presence of a carboxylic acid derivative is not mandatory, and other substrates such as 2-iodo diaryl ethers (Y = I) or the corresponding diazonium salts ($Y = N_2^+ BF_4^-$) can be used for the synthesis of xanthones in a palladium-catalysed carbonylation/C–H activation (section 4.1.2.5). Other kinds of cyclization strategies have also been reported in which the xanthone core can be obtained through a Co(I)-catalysed Barbier reaction of aromatic halides with aromatic aldehydes and imines,[156] a $PhI(OAc)_2$–BF_3–OEt_2 mediated domino imine activation, intramolecular C–C bond formation and β-elimination,[157] or a quaternary ammonium salt-promoted intramolecular dehydrogenative arylation of aldehydes.[158]

4.1.2.1 Cyclization of diaryl ethers to xanthones by a cross-dehydrogenative coupling. After the pioneering work of Wang *et al.*[159] in 2012 on the synthesis of xanthones *via* a rhodium-catalysed cross-dehydrogenative coupling (CDC) starting from 2-aryloxybenzaldehydes, alternative transition-metal catalysed strategies to construct the xanthone scaffold have been developed (Scheme 11)[160–163] For example, Wertz *et al.*[160] reported an elegant and straightforward procedure for the synthesis of the xanthone core through a $FeCp_2$-catalysed CDC reaction *via* a base-promoted homolytic aromatic substitution. Under the optimized conditions, several 2-aryloxybenzaldehydes bearing both electron-donating and electron-withdrawing substituents were coupled efficiently to give the corresponding xanthones with yields ranging from 30 to 78% (Scheme 11). Later, Manna *et al.*[161] reported an *ortho* C–H bond functionalization involving dichloro(*p*-cymene)ruthenium(II) dimer $[[RuCl_2(p\text{-cymene})_2]_2$ catalysed C–C bond formation. When compared to other metal-mediated CDC methodologies, this protocol does



Scheme 10 Synthesis of diaryl ether by Ullmann condensation.



Scheme 11 Methodologies for the synthesis of xanthones through intramolecular cross-dehydrogenative coupling (CDC) of 2-aryloxybenzaldehydes.

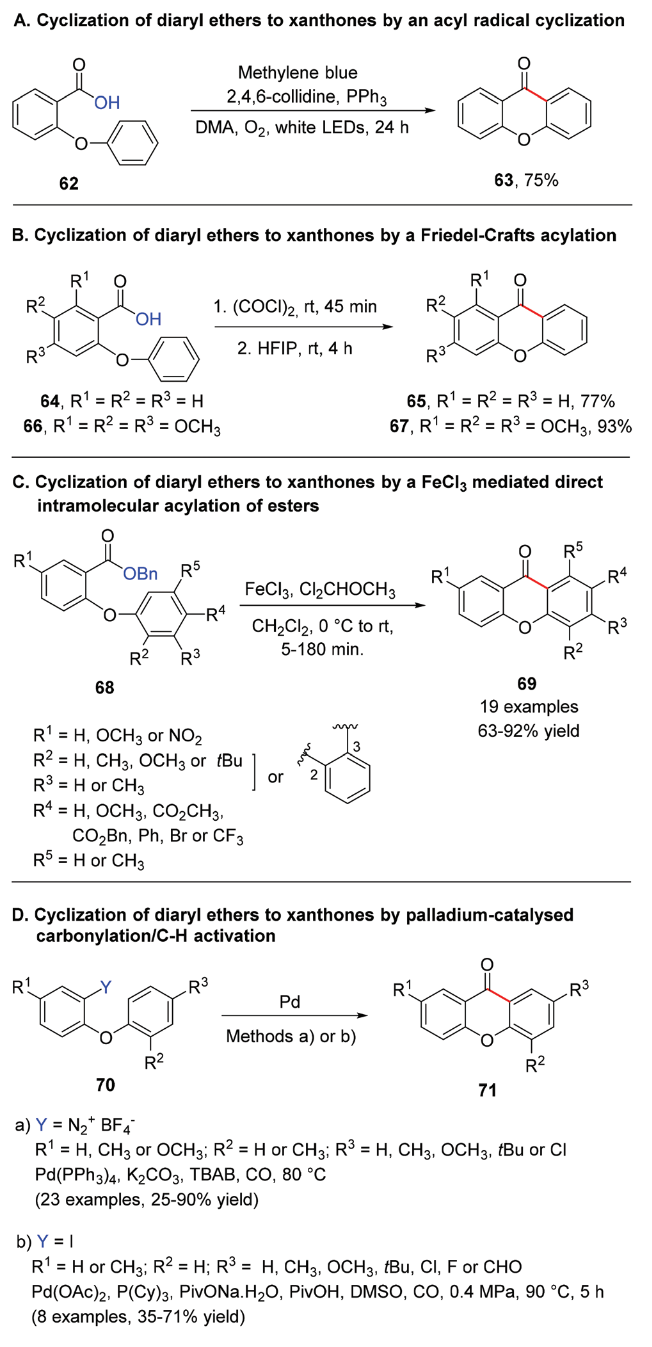
not require any expensive metal-catalyst and uses a commercially available cheap oxidant. The authors extended the scope of this reaction not only to xanthones, but also to thioxanthones and fluorenones in moderate to good yields.[161] Recently, Bao *et al.*[162] described a Cu(0)/Selectfluor system-catalysed intramolecular Csp^2–H/Csp^2–H bond CDC of 2-aryloxybenzaldehydes (Scheme 11).

Interestingly, when in the presence of a substituent in the *ortho* position to the formyl group on the 2-aryloxybenzaldehyde, regioisomers were obtained. The presence of substituents at the *ortho*, *meta*, or *para* positions relatively to the formyl group are well tolerated, the products being obtained in good yields, except in the case of OPh, affording the desired product in lower yield (49%). Besides the clear advantages related to the use of an inexpensive and low-toxic copper catalyst and relatively mild reaction conditions, this procedure also accepts a wide variety of substituent groups such as F, Cl, Br, OCF_3, CF_3, Ph, OPh, iPr, and iBu, which provides opportunities for further molecular modifications. The authors were able to expand the use of this methodology for the synthesis of 9*H*-thioxanthen-9-one and 10,10-dioxide and phenanthridin-6(5*H*)-one derivatives[162] and, interestingly, this process could be conducted successfully on a gram scale for a simple oxygenated xanthone (80% yield). A plausible mechanism for the $[RuCl_2(p\text{-cymene})_2]_2$-catalysed cyclization reaction was proposed and involves the formation of a cyclic seven membered transition state by addition of TBHP followed by reductive elimination to afford the desired compounds **61**.[161]

Over the last few years, the development of green CDC methodologies has sprout in order to compete with these transition-metal catalysed approaches (Scheme 11) and to address some drawbacks of their use in the pharmaceutical industry (metal harsh elimination and consequent toxicity). Rao *et al.*[164] reported a metal-free tetrabutylammonium bromide (TBAB)-promoted intramolecular annulation in aqueous medium, *via* oxidative coupling of C–H bond/aromatic C–H of several 2-aryloxybenzaldehydes. After reaction condition optimization, this reaction tolerated both electron-donating and electron-withdrawing functional groups (Scheme 11). Interestingly, when 2-(4′-phenoxyphenoxy)-benzaldehyde was employed, the formyl C–H bond selectively coupled with the 2-phenoxy part to give the phenoxy-9*H*-xanthen-9-one while leaving the 4′-phenoxy part intact, attesting that the intramolecular route is favored by the oxidative coupling protocol.

In a related investigation, Tang *et al.*[165] developed a straightforward ring closure protocol for the synthesis of xanthones from 2-aryloxybenzaldehydes through a simple and practical carbon tetrabromide promoted intramolecular aerobic oxidative dehydrogenative coupling reaction (Scheme 11). The scope and versatility of this reaction were also investigated, by experimenting different solvents, halogen reagents, and substituents, with good tolerance for different functional groups, being inclusively extended for the synthesis of fluorenones by using 2-arylbenzaldehydes as substrates. After preliminary studies on the reaction mechanism, the authors also suggested that the reaction may proceed through a radical pathway.[165]

4.1.2.2 Cyclization of diaryl ethers to xanthones by an acyl radical cyclization. Although CDC is the most frequently used methodology for the synthesis of xanthones from diaryl ethers, other less explored methodologies, with substrates containing a carboxylic acid derivative moiety, have recently been reported. An efficient intramolecular radical cyclization reaction *via* photoredox catalysis was developed for the synthesis of dibenzocycloketone derivatives using methylene blue as a photosensitizer (Scheme 12A).[166] This strategy relies on the fact that carboxylic acids are attractive and widely used syn-



Scheme 12 Methodologies used for the cyclization of diaryl ethers to xanthones.

thons to prepare acyl radicals by decarboxylation through photoredox catalysis. The authors used 2-(2-phenoxyacetyl) benzoic acid as a model substrate to obtain the corresponding eight-membered dibenzocycloketones and, after reaction condition optimization, the scope of the reaction was extended to other six, seven and eight-membered dibenzocycloketones. Xanthone (**63**) was obtained in 75% yield through a reaction of 2-phenoxybenzoic acid (**62**) with methylene blue, PPh_3 and 2,4,6-collidine in 2 mL DMA and irradiated with LED white light at 25 °C for 24 h.[166]

4.1.2.3 Cyclization of diaryl ethers to xanthones by a Friedel–Crafts acylation. A promising metal-free variant of the intramolecular Friedel–Crafts acylation reaction, which employs mild conditions and avoid excesses of harsh acids, was described by Motiwala *et al.*[167] This simple strategy consists of dissolving readily available acid chlorides in 1,1,1,3,3,3-hexafluorpropan-2-ol (HFIP), a strong hydrogen-bond-donating solvent, and allows the reaction to stir at room temperature for 4 h (Scheme 12B). The reaction was optimized using 4-(3,4-dimethoxyphenyl)butanoic acid as a model against solvent, HFIP loading, and reaction time to obtain 6,7-dimethoxy-1-tetralone. After the optimal conditions were obtained, the scope was extended to a range of structurally diverse carboxylic acids; the formation of six-membered rings was generally favored over five- and seven-membered rings, xanthone **65** being obtained in 77% yield and 1,2,3-trimethoxy-9*H*-xanthen-9-one (**67**) in 93% yield (Scheme 12B).

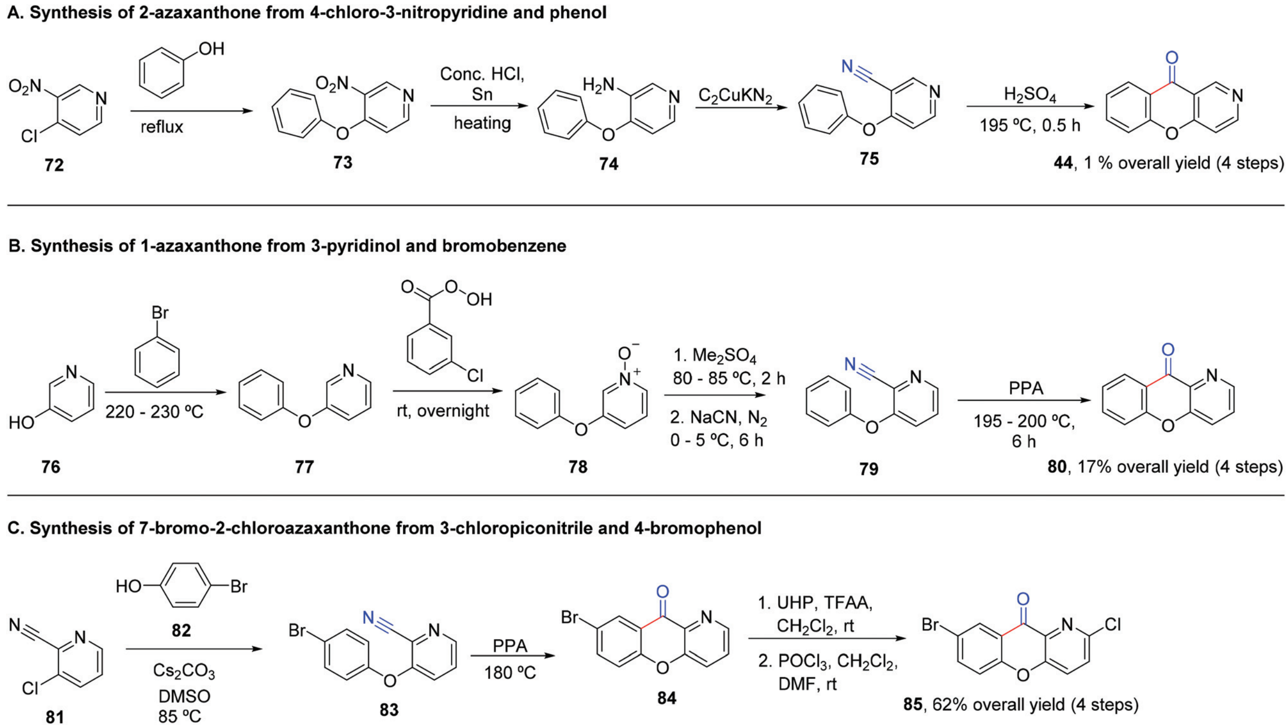
4.1.2.4 Cyclization of diaryl ethers to xanthones by a $FeCl_3$ mediated direct intramolecular acylation of esters. Benzyl esters have also shown to be suitable building blocks for the synthesis of xanthone derivatives. This serendipitous example of cyclization of diaryl ethers bearing a carboxylic acid moiety emerged as a way to dodge the disadvantages sometimes associated with the classical methods.[168] After an initial screening concerning several catalysts, dichloromethyl methyl ether loading, and reaction times, and with the optimal conditions in hand, the scope of the reaction was investigated and it was observed that the acylation could tolerate various functional groups such as OCH_3, NO_2, CO_2CH_3, Br, and Cl, affording the desired xanthones in good yields (Scheme 12C). Mechanistic studies indicated that the formation of an intermediate, which results from the cooperative activation of benzyl esters by $FeCl_3$ and Cl_2CHOCH_3, plays a key role in the acylation of esters.

4.1.2.5 Cyclization of diaryl ethers to xanthones by palladium-catalysed carbonylation/C–H activation. Although the previous examples approached the use of diaryl ethers bearing a carboxylic acid moiety, this is not mandatory and the carbonyl bridge between the two aryl rings can be formed with the aid of carbon monoxide. Thus, palladium catalysed carbonylations/C–H activation reactions emerged as an alternative methodology for the synthesis of xanthones in the last few years. The employment of a palladium catalyst (and ligand), base/additive, and carbon monoxide proceeds smoothly when using 2-iodo diaryl ethers or the corresponding diazonium salts to form the desired xanthones, with great tolerance for different functional groups (Scheme 12D). The proposed mechanism of the intramolecular cyclization is similar in both strategies and proceeds through the initial oxidative addition of Pd, insertion of CO, activation of an *ortho* aromatic C–H with the assistance of the base, subsequent reductive elimination to afford the intended xanthone, and regeneration of Pd for the next catalytic cycle.

4.2 Synthesis of azaxanthones

The synthesis of azaxanthones *via* the diaryl ether route requires the synthesis of an intermediate, typically a cyanopyridyl phenyl ether (Scheme 13) or a phenoxynicotinic acid derivative (Scheme 14). Cyanopyridyl phenyl ether derivatives can be obtained either through S_NAr of aromatic halides with hydroxypyridine or phenol derivatives. Phenoxynicotinic acids are also achieved *via* S_NAr, from building blocks containing the carboxylic acid moiety or other functionalities (*e.g.* methyl) that are easily converted into the desired carboxylic acid. Other strategies include the use of quinolinimide as the starting material, which can be further transformed into the corresponding carboxylic acid (Scheme 14). An excess of protic acid (often as solvent) such as sulfuric acid or polyphosphoric acid (PPA) is usually the reagent of choice for the intramolecular Friedel–Crafts cyclization reaction.

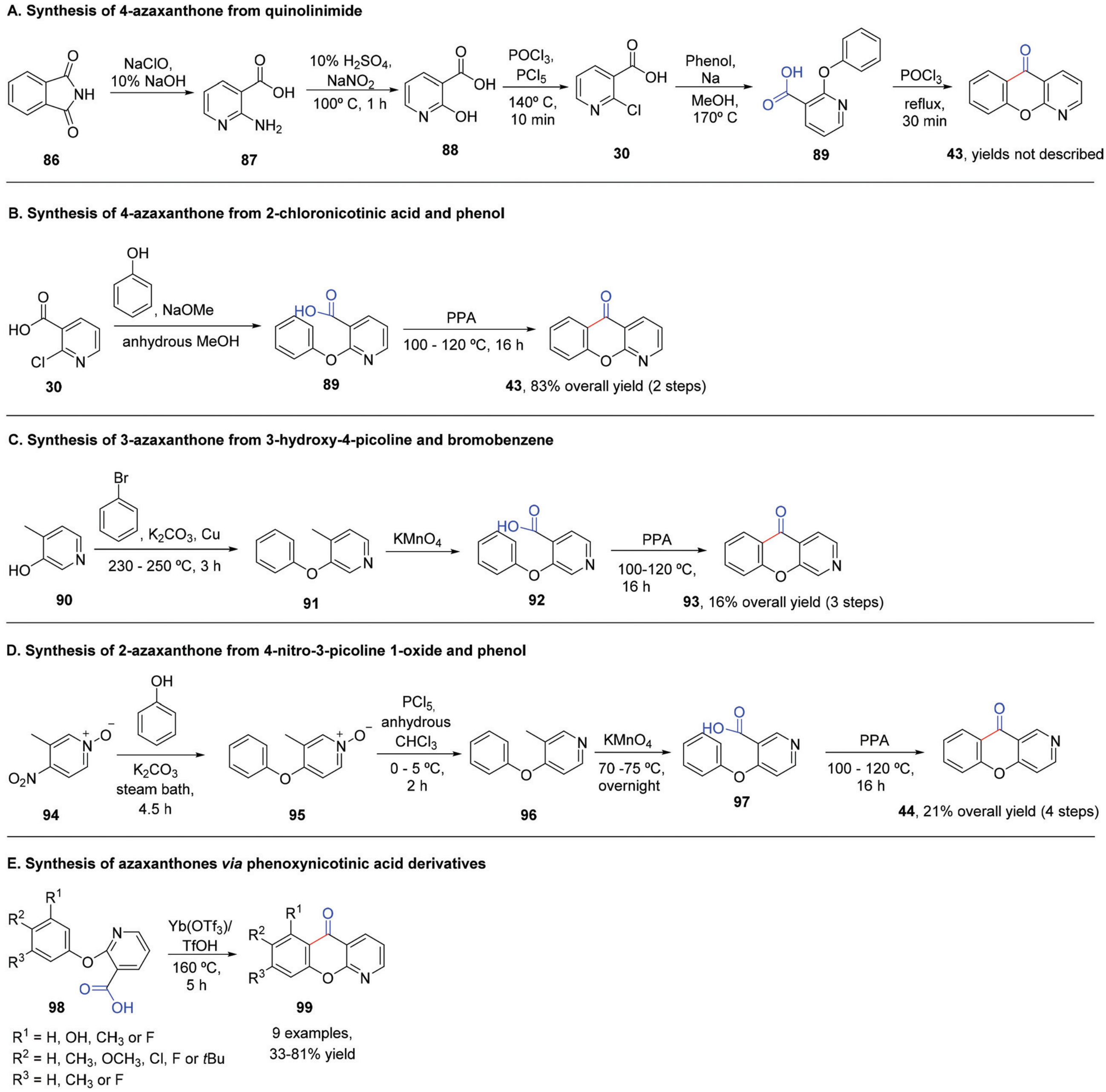
4.2.1 Synthesis of azaxanthones *via* cyanopyridyl phenyl ether. The synthesis of azaxanthones *via* cyanopyridyl phenyl ether is a very straightforward methodology, since the cyclization step is easily achieved due to the presence of a pendent cyano moiety. 2-Azaxanthone (**44**) was synthesized *via* this methodology by Kruger *et al.*,[169] starting from the condensation of 4-chloro-3-nitropyridine (**72**) with phenol to yield intermediary 3-nitro-pyridyl phenyl ether (**73**) (Scheme 13A). Reduction of the nitro group, oxidative conversion of the amine to the corresponding nitrile, and further cyclization with sulfuric acid at 195 °C led to 2-azaxanthone (**44**), in very low yield (1% over 4 steps), probably due to the formation of sulfonated phenoxy derivatives that were soluble in water. A similar strategy was used for the synthesis of 1-azaxanthone (**80**)[78] (Scheme 13B). 3-Phenoxypyridine (**77**) was used as the starting material, previously obtained from the reaction between 3-pyridinol (**76**) and bromobenzene. *N*-Oxide formation with *m*-chloroperbenzoic acid, and the subsequent reaction with dimethyl sulfate produced *N*-methoxymethyl sulfate salts. Due to the fact that the resulting salts are generally hygroscopic and difficult to handle, a reaction with sodium cyanide under a nitrogen atmosphere yielded stable 2-cyano-3-phenoxypyridine (**79**). 1-Azaxanthone (**80**) was obtained *via* direct ring closure in 17% overall yield in four steps from 3-pyridinol (**76**). A di-halogen-substituted azaxanthone was also synthesized *via* cyanopyridyl phenyl ether from 3-chloropiconitrile (**81**) and 4-bromophenol (**82**) (Scheme 13C). The diaryl ether **83** was obtained through S_NAr and further intramolecular Friedel–Crafts reaction in PPA and an *in situ* hydrolysis yielded the 1-azaxanthone core **84**. Nitrogen oxidation and treatment with phosphoryl chloride originated the desired chloride **85** with 62% overall yield, considering 4 reaction steps (Scheme 13).[149]



Scheme 13 Synthesis of azaxanthones *via* cyanopyridyl phenyl ether derivatives (diaryl ether route).

4.2.2 Synthesis of azaxanthones *via* phenoxynicotinic acid derivatives. 4-Azaxanthone (**43**), also known as 9-oxa-4-aza-anthrone or 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one, was the first azaxanthone to be synthesized ever, following a methodology involving phenoxynicotinic acid derivatives (Scheme 14A). Preparation of 2-aminonicotinic acid (**87**) *via* the Hofmann reaction on quinolinimide **86** previously obtained from 8-hydroxiquinoline and further treatment of **87** with nitrous oxide yielded 2-hydroxynicotinic acid (**88**). Transformation into 2-chloronicotinic acid (**30**) and condensation of the corresponding sodium salt with sodium phenoxide yielded 2-phenoxynicotinic acid (**89**) which after cyclization afforded compound **43**.[170] Another method for the synthesis of azaxanthones was developed by Villani and collaborators,[78] taking phenoxypyridinecarboxylic acids as the starting materials, with the nitrogen in different positions, according to the desired azaxanthone. The reactions employed allowed the synthesis of azaxanthones previously described in better yields. For the synthesis of 4-azaxanthone (**43**, Scheme 14B), 2-chloronicotinic acid (**30**) reacted with phenol in the presence of sodium methoxide to yield 2-phenoxynicotinic acid (**89**). The ring closure was achieved with the use of phenylphosphonic acid (PPA), in 83% overall yield [2 steps from 2-chloronicotinic acid (**30**). For the synthesis of 3-azaxanthone (**93**, Scheme 14C), the starting materials used were 3-hydroxy-4-picoline (**90**) and bromobenzene, which through the Ullmann condensation led to 3-phenoxy-4-picoline (**91**). 3-Phenoxyisonicotinic acid (**92**) was obtained by oxidation of **91** and heating of **92** with PPA, similarly to the previous reaction, led to 3-azaxanthone (**93**) in 16% overall yield, in three steps from 3-hydroxy-4-picoline (**90**).[78] On the other hand, 2-azaxanthone (**44**) was prepared by using 4-nitro-3-picoline 1-oxide (**94**) and phenol as the starting materials. Displacement of the nitro group by phenoxide in the presence of K_2CO_3 gave phenyl ether **95** that was *N*-deoxygenated to the pyridyl ether **96.** Oxidation gave the desired 4-phenoxynicotinic acid (**97**) which after ring closure gave 2-azaxanthone (**44**) in 21% overall yield in 4 steps from 4-nitro-3-picoline 1-oxide (**94**) and phenol (Scheme 14D).[78] Worth highlighting is a simple and clean methodology for the synthesis of azaxanthones and azathioxanthones. Li *et al.*[171] developed a synthetic route that did not use expensive materials and had solvent-free conditions, starting from phenoxypyridine acids. In order to obtain the best catalyst, studies with a series of metal triflates were carried out. It was concluded that ytterbium(III) trifluoromethansulfonate was the best catalyst, and that the use of a Brønsted acid would slightly improve the yield in the synthesis of 4-azaxanthone and derivatives (Scheme 14E).

4.2.3 Synthesis of azaxanthones *via* amide derivatives. In an effort to find new β-amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors, new azaxanthones were synthesized.[149] Compared to previously synthesized xanthones, the introduction of a nitrogen could improve *in vitro* potency, cardiovascular safety, pharmacokinetics, and drug metabolism, and modulate central nervous system penetration.[172] These features could also be evidenced by a fluorine-substitution at the 3- or 4-position. The combination of these features would ultimately lead to an overall improvement of the compounds as BACE1 inhibitors. Since these molecules had never been synthesized before, different synthetic approaches were attempted.

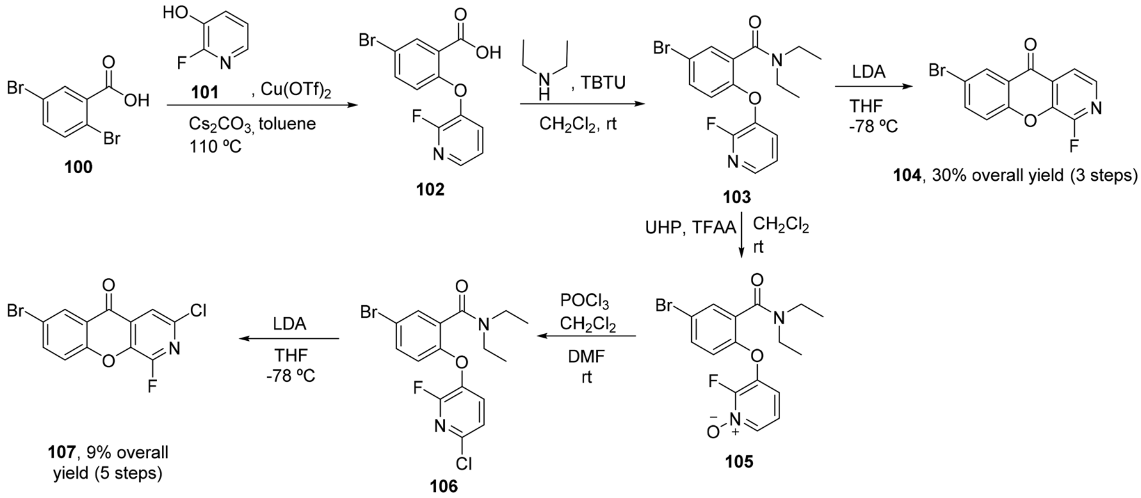


Scheme 14 Synthesis of azaxanthones *via* phenoxynicotinic acid derivatives (diaryl ether route).

For the synthesis of 3-aza-4-fluoroxanthone **104** (Scheme 15), the first step was the regioselective copper-catalysed Ullmann coupling between 2,5-dibromobenzoic acid (**100**) and 2-fluoro-hydroxypyridine (**101**), which afforded a diaryl ether **102**. This intermediate **102** was treated with diethylamine and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoro-borate (TBTU) to give amide **103**. An amide-directed lithiation on the pyridine, followed by an *in situ* cyclization furnished a fluorinated azaxanthone **104** [30% overall yield in 3 reaction steps from 2,5-dibromobenzoic acid (**100**)]. From the same amide intermediate **103**, *N*-oxidation was performed on the pyridine nitrogen (**105**) and subsequent treatment with phosphoryl chloride afforded a chloride derivative **106**, which produced a tri-halogenated azaxanthone **107** after a tandem lithiation/cyclization (Scheme 15), with an overall yield of 9% in five steps from 2,5-dibromobenzoic acid (**100**) and 2-fluoro-hydroxypyridine (**101**) (Scheme 15).[149]

5 Synthesis of (aza)xanthones *via* chromone derivatives

The chromone core constitutes a versatile building block that can be used for the synthesis of xanthone derivatives. To form



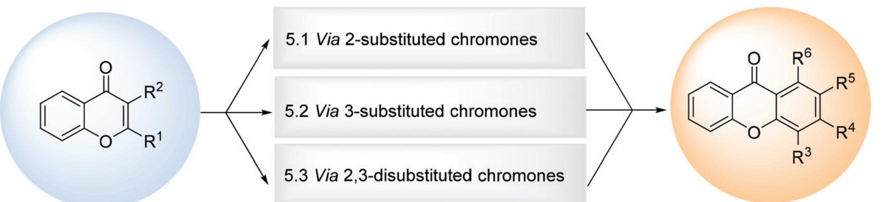
Scheme 15 Synthesis of azaxanthones *via* amide derivatives (diaryl ether route).

an additional aromatic ring, several strategies can be applied, mainly the traditional Diels–Alder or other cycloaddition reactions. Depending on the substitution pattern of the chromone derivative, this section will be sub-divided into three subsections: synthesis of xanthones from 2-substituted (section 5.1), 3-substituted (section 5.2) and 2,3-disubstituted chromones (section 5.3) (Scheme 16).

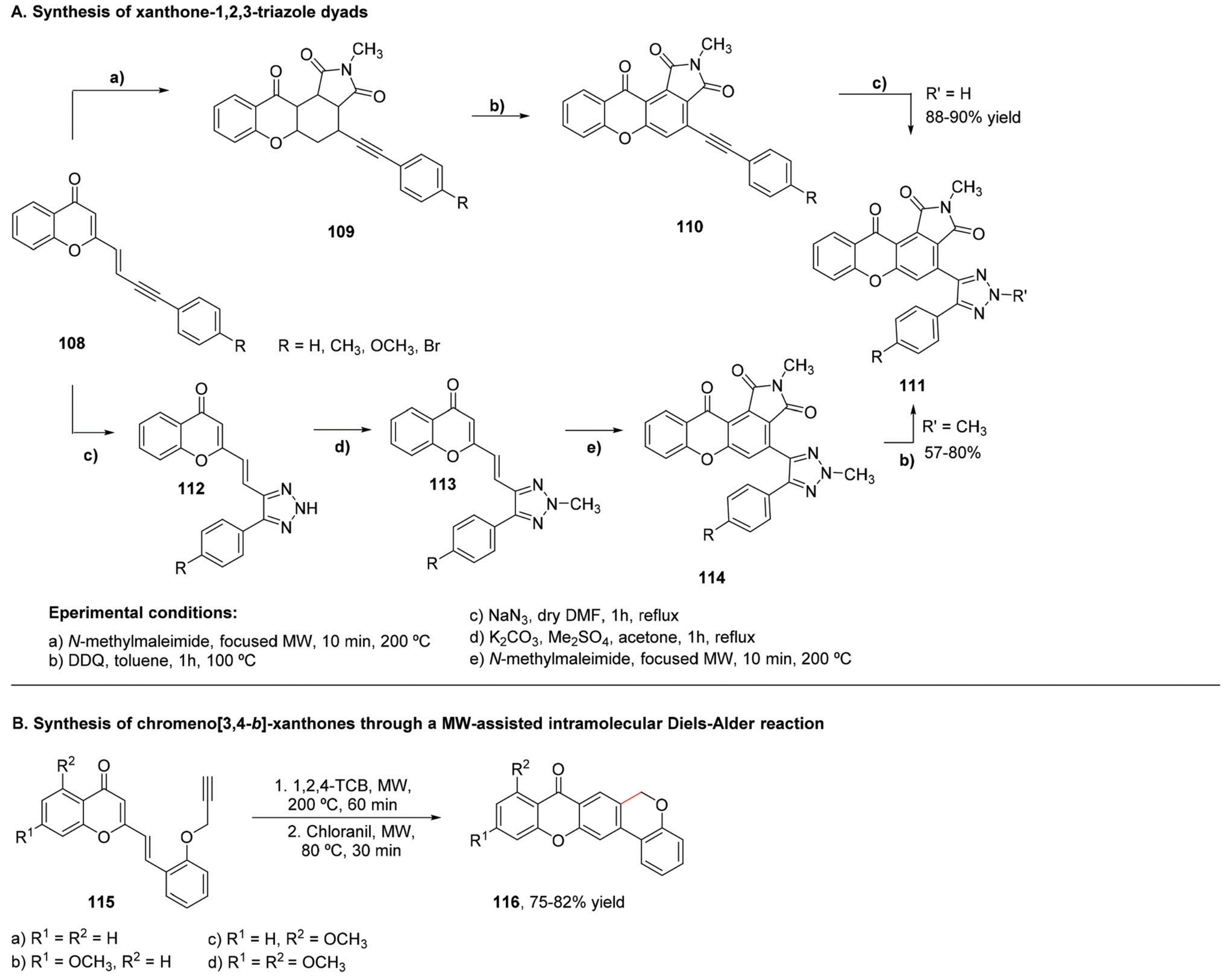
5.1 Synthesis of xanthones from 2-substituted chromones

5.1.1 *Via* Diels–Alder reaction. The high versatility and efficiency of the Diels–Alder reactions have also been extended to the synthesis of xanthones from 2-substituted chromones. Xanthone-1,2,3-triazole dyads were obtained by two different approaches, both starting from (*E*)-2-(4-arylbut-1-en-3-yn-1-yl) chromones, previously obtained by a base-catalysed aldol reaction of 2-methylchromone and arylpropargyl aldehydes.[173] While the first approach adopted a methodology in which the xanthone core is primarily constructed using chromones as dienes in the Diels–Alder reaction, followed by the construction of the triazole ring, in the second strategy the process was inverted, staring with the triazole ring followed by the construction of the xanthone core (Scheme 17A). Thus, in the first methodology, a Diels–Alder reaction of the chromone derivatives **108** with *N*-methylmaleimide under microwave irradiation gave Diels–Alder adducts **109.** Oxidation of the obtained adducts with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave xanthone derivatives **110** which upon reacting with sodium azide in refluxing DMF provided the desired xanthone-1,2,3-triazole dyads **111** in excellent yields (88–90%). The second approach consisted of a 1,3-cycloaddition reaction of chromones **108** with sodium azide to form the triazole derivatives (**112**) followed by methylation of the triazole NH group prior to the Diels–Alder reaction with *N*-methylmaleimide and oxidation with DDQ to provide the xanthone-1,2,3-triazole dyads (**111**) in moderate to good yields (57–80%).[173] (*E*)-2′-Propargyloxy-2-styrylchromones (**115**) were used as substrates in a microwave-assisted intramolecular Diels–Alder reaction, affording chromeno[3,4-*b*]-xanthones **116** (Scheme 17B).[174] During optimization processes, besides the variation of solvent, Lewis acid, temperature, and reaction time, different oxidizing agents were also tested in order to push the reaction towards the oxidized product **116**, without the formation of secondary products that are not fully oxidized. Optimal conditions for MAOS of chromeno[3,4-*b*]xanthones are the use of 1,2,4-trichlorobenzene (1,2,4-TCB) as a solvent, under MW irradiation at 200 °C for 60 min and then the addition of the oxidizing agent chloranil to the reaction crude, under MW irradiation at 80 °C for 30 min.[174]

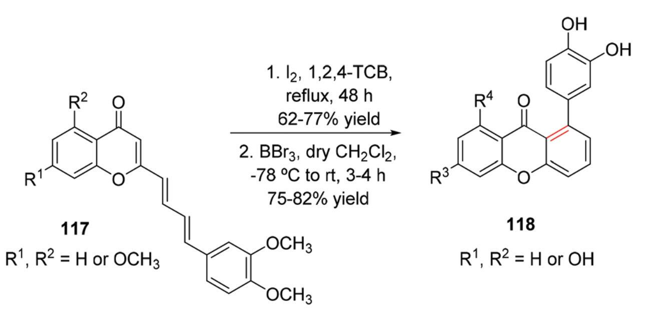
5.1.2 *Via* electrocyclization. Another example of transforming 2-substituted chromones into xanthone derivatives is through an electrocyclization and subsequent oxidation (Scheme 18). The substrates 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-



Scheme 16 Synthesis of xanthones *via* chromones.



Scheme 17 Synthesis of xanthones from 2-substituted chromones *via* the Diels–Alder reaction.

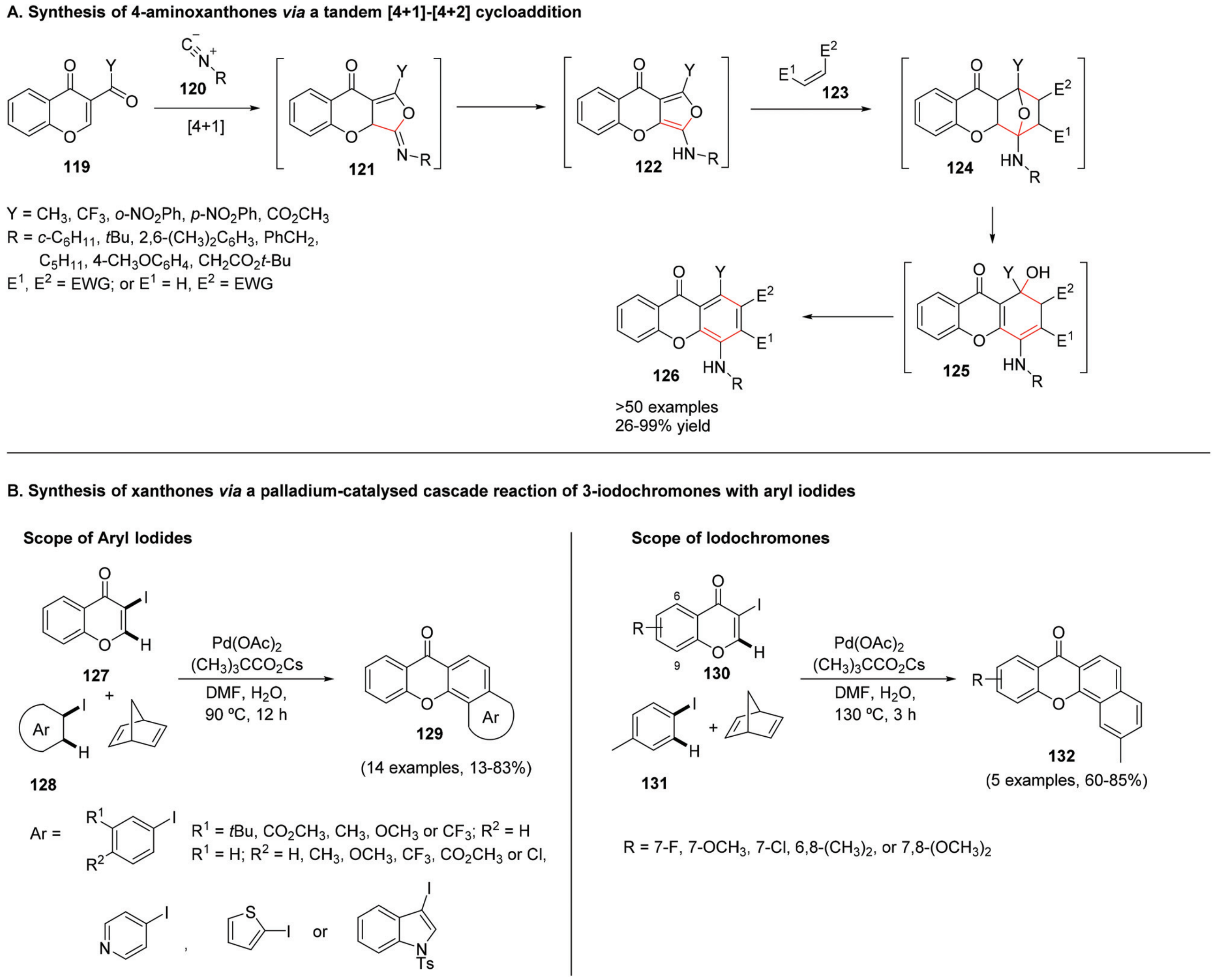


Scheme 18 Synthesis of xanthones through an electrocyclization and subsequent oxidation.

4*H*-chromone **117** are previously obtained in good yields by condensation of 2-methyl-4*H*-chromones with cinnamaldehydes in the presence of sodium ethoxide. Thus, the target 1-aryl-9*H*-xanthen-9-ones **118** are obtained under refluxing 1,2,4-TCB in the presence of a catalytic amount of iodine and subsequent demethylation with BBr_3, in moderate to good yields.[175] This study also disclosed that some of the tested compounds had improved scavenging activity when compared with previously reported analogues, being promising pharmacophores with potential therapeutic applications associated with oxidative stress disorders.[175]

5.2 Synthesis of xanthones from 3-substituted chromones

5.2.1 *Via* a tandem [4 + 1]-[4 + 2] cycloaddition. Bornadiego *et al.*[176–178] reported the synthesis of 4-aminoxanthones *via* a tandem [4 + 1]-[4 + 2] cycloaddition of 3-carbonylchromones, isocyanides and dienophiles (Scheme 19A). The authors were able to extend the reaction scope to different dienophiles, either symmetric *N*-phenyl- and *N*-methylmaleimide, maleimide, and maleic anhydride,[176] or asymmetric ones like acrylonitrile or methyl vinyl ketone.[177] Additionally, they were also able to extend this methodology to carbonylchromones containing both electron-withdrawing and electron-donating groups.[178] Mechanistically, 4-aminoxanthone is obtained through a [4 + 1] cycloaddition of a 3-carbonylchromone **119** with an isocyanide **120** to give an iminolactone intermediate

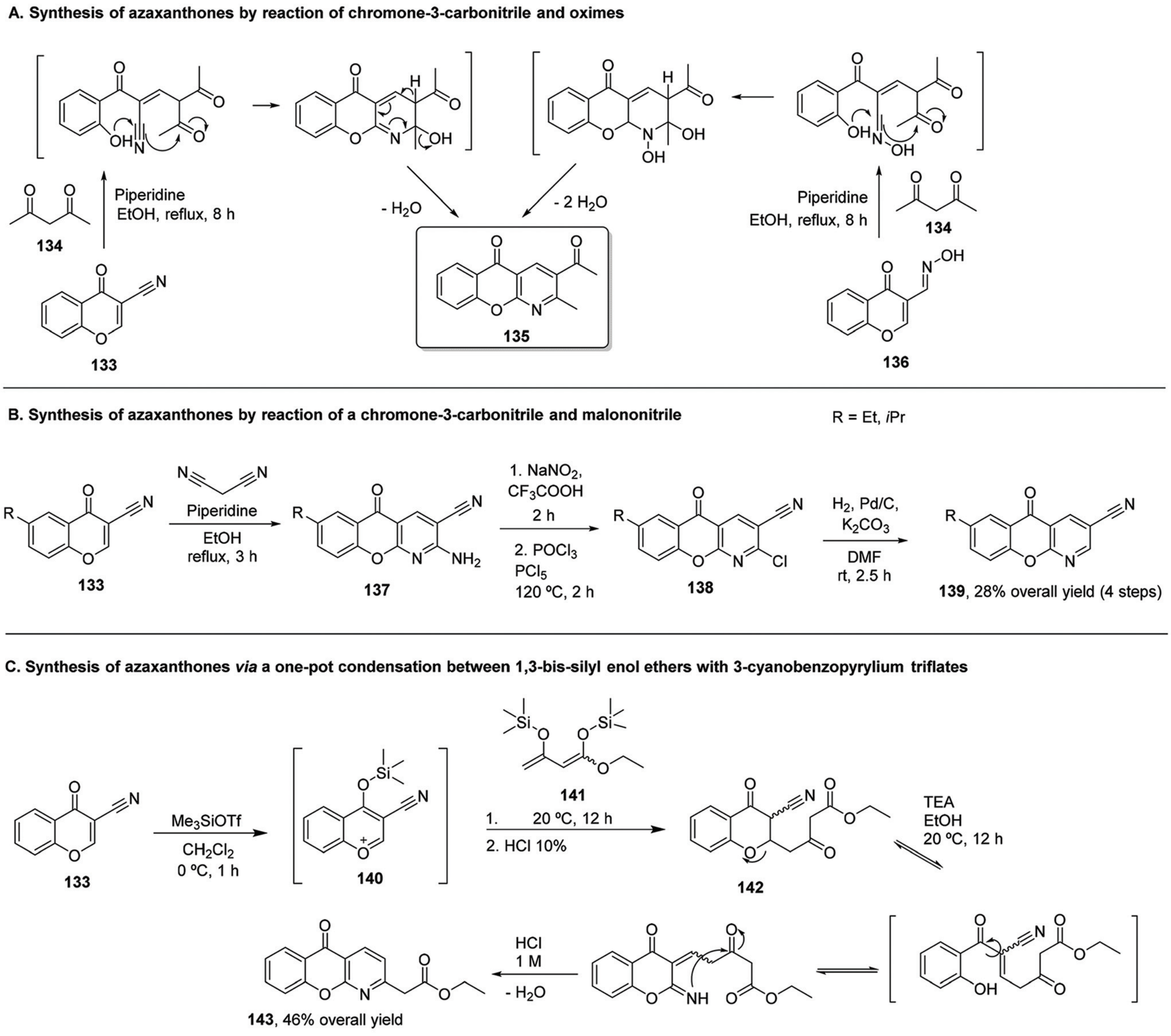


Scheme 19 Synthesis of xanthones from 3-substituted chromones.

121. Tautomerization to aminofuran **122**, which undergoes a [4 + 2] cycloaddition with the dienophile **93**, leads to 7-oxabicyclo [2.2.1]heptane (**124**). This is readily transformed to 1-hydroxydihydroxanthone **125** by the opening of the oxygen bridge assisted by the nitrogen lone pair. Dehydration finally affords the aromatic 4-aminoxanthone **126** (Scheme 19A).[178]

5.2.2 *Via* a tandem Heck reaction/double C–H activation/retro Diels–Alder pathway. Another strategy towards the construction of the xanthone core from 3-substituted chromones is *via* a tandem Heck reaction/double C–H activation/retro Diels–Alder pathway. The use of readily available 3-iodochromones **127** and **130**, aryl iodides **128** and **131**, and norbornadiene as the starting materials in this palladium-catalysed cascade reaction enables access to diverse annulated xanthones (**129** and **132**, Scheme 19B).[179] This process is initiated by oxidative addition of Pd(0) to the chromone ring system, followed by norbornadiene insertion and C–H activation of the 2-position of the chromone ring. A second oxidative addition of the aryl iodide, subsequent reductive elimination, and second C–H activation formed the desired xanthones.[179]

5.2.3 Synthesis of azaxanthones by reaction of carbonitrile chromones and oximes. To better understand the condensation reactions of chromone-3-carbonitriles, Ghosh *et al.*[180] have performed reactions that yielded, among other compounds, azaxanthones. The starting carbonitrile chromone **133** reacted with acetylacetone (**134**), in the presence of piperidine, furnishing a 4-azaxanthone derivative **135** in 80% yield. The mechanism through which this reaction occurs was investigated, and it was concluded that **134** undergoes Michael addition to the α,β-unsaturated ketone. Concomitantly, the pyrone ring opens, yielding an intermediate which undergoes, probably in a concerted manner, a double cyclisation (Scheme 20A). The same study also contemplated the synthesis of the same compound (**135**), taking an oxime (**136**) as the starting material (Scheme 20A). Given that chromone-3-nitriles are prepared from oximes, their use for preparing azaxanthones shortens the synthetic route, although the yield,



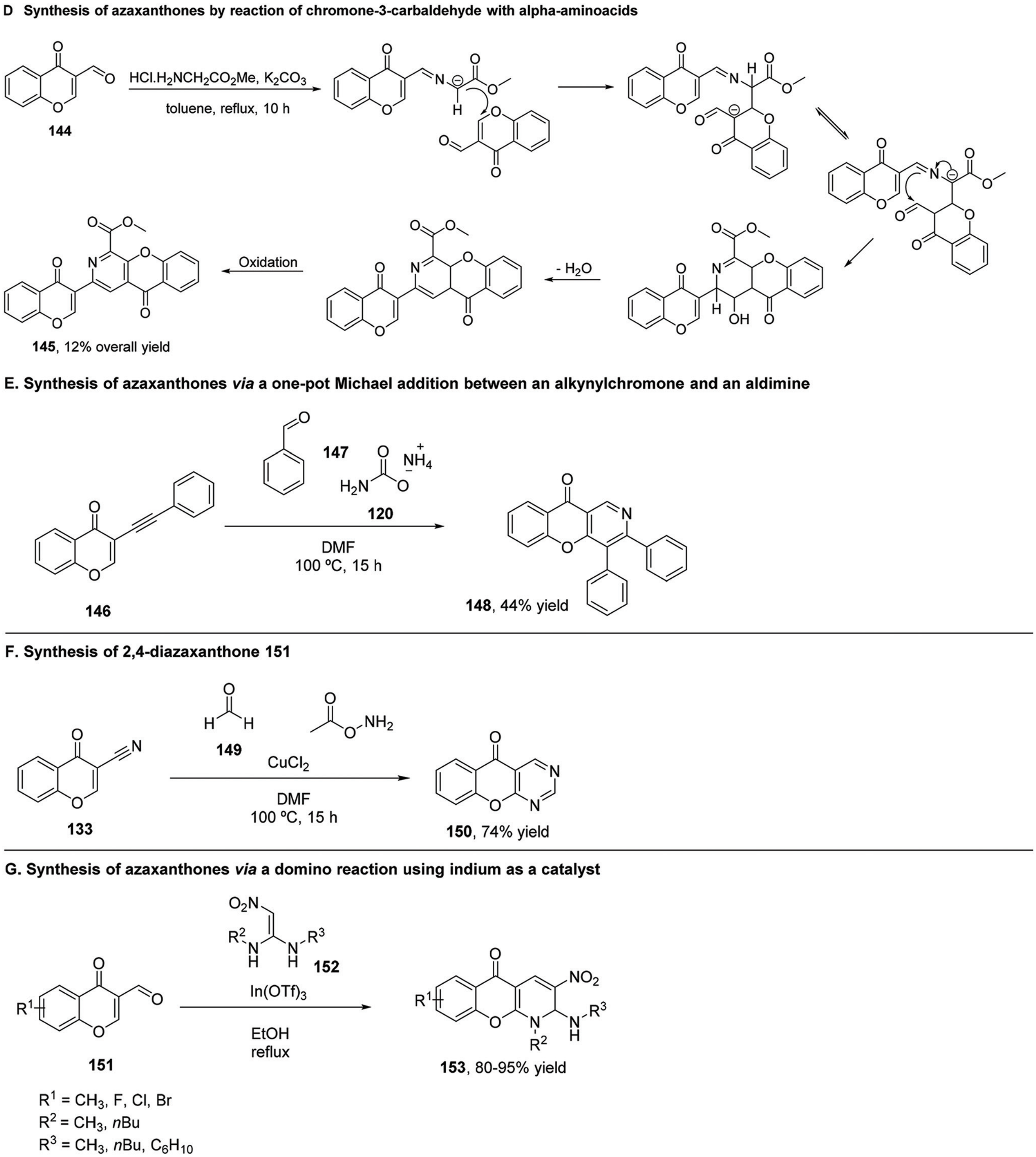
Scheme 20 Synthesis of azaxanthones from 3-substituted chromones.

67%, was not as good as when the nitrile was used as the starting material.[180]

5.2.4 Synthesis of azaxanthones by reaction of a cyano chromone and malononitrile. A reaction of cyano chromone **133** with malononitrile led to **137** which was then deaminated by sodium nitrite in trifluoroacetic acid. Further chlorination using phosphoryl chloride and phosphorus pentachloride afforded **138** in 38% yield, which was converted to compound **139** by catalytic hydrogenation (Scheme 20B), in 28% overall yield from cyano chromone **133** in four reaction steps.[181]

5.2.5 Synthesis of azaxanthones *via* a one-pot condensation between 1,3-bis-silyl enol ethers with 3-cyanobenzopyrylium triflates. Azaxanthone derivatives could also be attained by domino reactions in a one-pot process. The approach used by Langer and Appel[182] consisted of the condensation of 1,3-bis-silyl enol ethers (**141**), unsymmetrical acetoacetone, with 3-cyanobenzopyrylium triflates (**140**). This yielded an open-chained product (**142**), which was treated with triethylamine, to give an azaxanthone (**143**) in 46% overall yield, through a domino "retro-Michael-lactonization-aldol" reaction (Scheme 20C).

5.2.6 Synthesis of azaxanthones by reaction of chromone-3-carbaldehyde with α-amino acids. In an attempt to synthesize (hydroxybenzoyl)pyrroles, Figueiredo *et al.*[183] have discovered an azaxanthone, from a chromone moiety. The reaction started with a chromone aldehyde **144** and ethyl glycinate hydrochloride, and depending on the reaction conditions, several compounds were formed. For the azaxanthone derivative **145** to be synthesized, in 12% overall yield, one equivalent



Scheme 20 *(Contd)*.

of methyl glycinate and 0.5 equivalent of potassium carbonate were required, in refluxing toluene. The authors proposed a mechanism for the formation of the azaxanthone intermediate, which comes from the oxidation of the dihydroxanthenone (Scheme 20D).

5.2.7 **Synthesis of azaxanthones *via* a one-pot Michael addition between an alkynylchromone and an aldimine.** One-pot approaches were also an efficient method of obtaining azaxanthones. In this scope, the starting material chosen was 2-(1-alkynyl)-2-alken-1-ones (Scheme 20E), which are interesting for multicomponent reactions, as they are prone to transition metal, Lewis acid, and electrophile-induced cascade cyclization reactions promoted by nucleophiles. Since these starting compounds have previously been reported to be involved in reactions initiated by Michael addition of nitrogen, it was postulated that *N*-unsubstituted aryl aldimines would act as nucleophiles in Michael addition reactions with 3-(1-alkynyl)chromones. Subsequently, a cascade sequence would be initiated, ultimately leading to the production of azaxanthones.[14] The optimal conditions for this reaction were also investigated. DMF was found to be the best solvent, against ethanol, DMSO, toluene, and dioxane. As for the base, it was shown that three equivalents of ammonium acetate provided the optimal conditions, but the reaction also occurred with ammonium carbamate, ammonium bicarbonate, and ammonium formate. In the opposite way, ammonium chloride and ammonium sulfate did not yield the desirable product.[14] The same study also described the synthesis of 2,4-diazaxanthones (**150**) through the same methodology (Scheme 20F). In an effort to extend the cascade reaction to other Michael acceptors, 3-cyanochromone (**133**) was chosen as the starting material. After testing different reaction conditions, it was demonstrated that the use of copper(II) chloride as an oxidant would lead to yields up to 85%. For the production of the unsubstituted 2,4-diazaxanthone (**150**), the aldehyde employed was paraformaldehyde (**149**), and the yield was 74% (Scheme 20F).[14]

5.2.8 Synthesis of azaxanthones *via* a domino reaction using indium as a catalyst. A green approach for the formation of azaxanthones was proposed by Poomathi *et al.*[184] This group managed to synthesize azaxanthones through a domino reaction using a small amount of catalyst and ethanol as the solvent. Studies on the catalyst showed that indium triflate was the best choice for a Lewis acid for this reaction, and that it could be recovered after the reaction and maintain its catalytic efficiency for, at least, five reactions.

In order to obtain azaxanthones (**153**), 3-formylchromones (**151**) reacted with *N*,*N*′-dibutyl-2-nitroethene-1,1-diamines (**152**), using $In(OTf)_3$ in ethanol, in reflux, as can be seen in Scheme 20G. This reaction allowed the synthesis of a series of derivatives, whose yields ranged from 80% to 95%.[184] The reaction mechanism hypothesized involves a Henry reaction between 3-formylchromone (**151**) and *N*,*N*-dibutyl-2-nitroethene-1,1-diamine (**152**) (Scheme 20G). Elimination of water and further 6π-electrocyclization yield azaxanthones **153**.[184]

5.3 Synthesis of xanthones from 2,3-disubstituted chromones

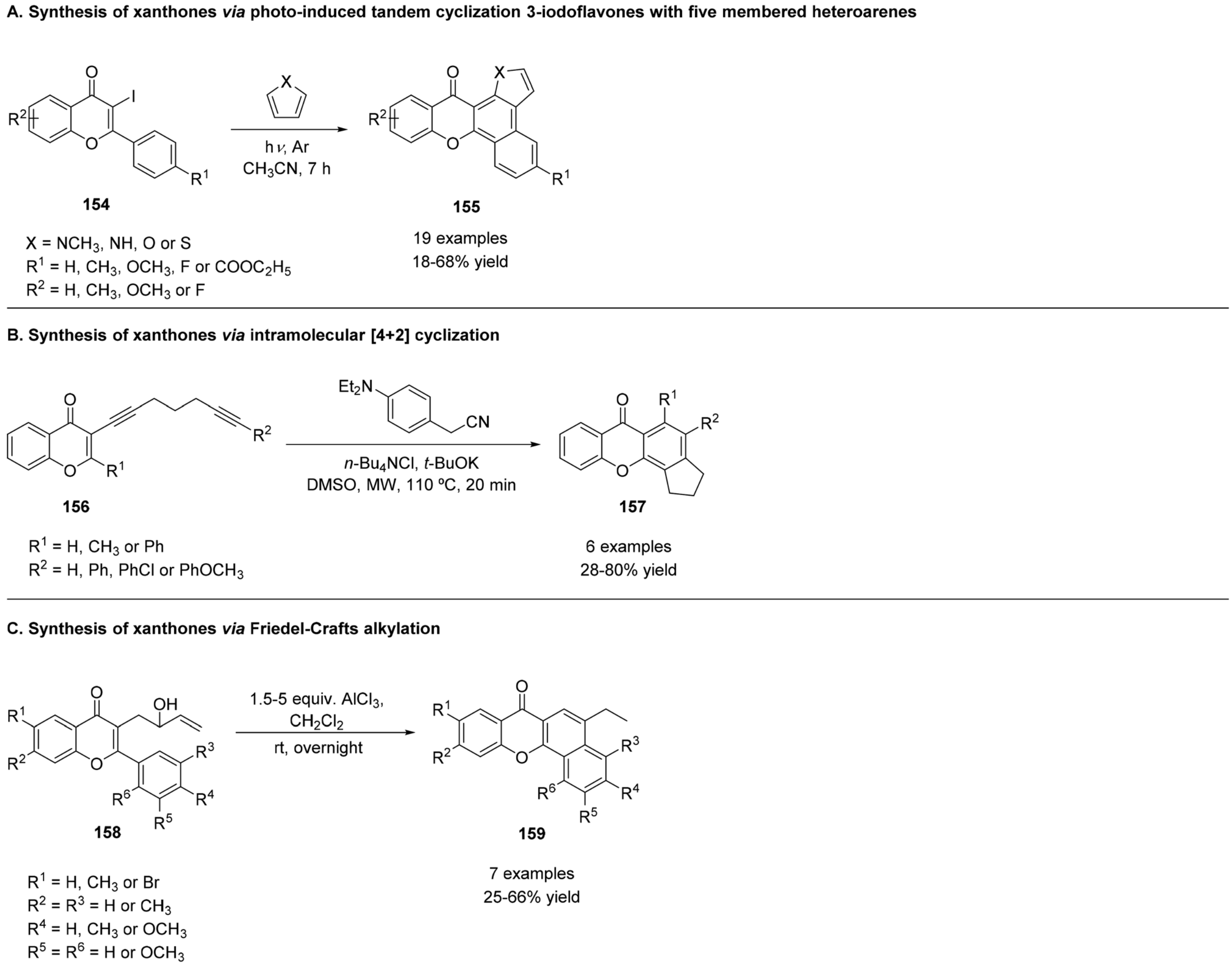
5.3.1 *Via* photo-induced tandem cyclization of 3-iodoflavones with five membered heteroarenes. An excellent example that provides rapid access to polycyclic xanthones without the requirement of any transition-metal-catalyst and/or oxidant additives is a tandem cyclization *via* the coupling of 3-iodoflavones **154** with five-membered heteroarenes.[185] This procedure allowed the preparation of a broad variety of novel polycyclic xanthone frameworks with excellent regioselectivity in good yields under mild and environmentally friendly reaction conditions. Mechanistic studies unveiled that the reaction proceeds *via* two consecutive C–C bond formations after irradiation of the substrate and *N*-methylpyrrole in CH_3CN using a high-pressure mercury lamp (500 W) at room temperature for 7 h (Scheme 20A). It was possible to observe that the obtained yields were lower when in the presence of electron-donating groups on both R^1 and R^2 and higher when in the presence of only one electron-donating group at either R^1 or R^2. The substrate scope was also extended to other five-membered heteroarenes, with the desired xanthone derivatives **155** being obtained in lower yields.[185]

5.3.2 *Via* intramolecular [4 + 2] cyclization. Another procedure that allows the preparation of xanthone derivatives without the need for a transition metal catalyst consists of a phase transfer reagent promoted tandem ring-opening and ring-closing reaction of 3-(hepta-1,6-diyn-1-yl)chromone derivatives **156** followed by a intramolecular [4 + 2] cyclization.[186] The use of *t*-BuOK, *n*-Bu_4NCl and phenylacetonitrile as an anion transfer reagent in DMSO at 110 °C for 20 min under MW irradiation proceeded smoothly for the preparation of several xanthone derivatives **157** (Scheme 21B), with the exception of R^2 = H, and R^1 = Ph, the latter probably due to the steric effects of two phenyl groups at the *ortho* position.[186]

5.3.3 *Via* Friedel–Crafts alkylation. An intramolecular Friedel–Crafts alkylation strategy using $AlCl_3$ in dichloromethane was used to smoothly synthesize the corresponding benzoxanthones **159** in low to moderate yields (Scheme 21C), with the more electron rich aromatic systems in the 2-position of the chromone **158** being obtained with increased efficiency.[187]

5.3.4 Synthesis of azaxanthones by reaction of chromone-3-carbonitriles and aminoacrylate or ethyl propiolate. While performing studies on potential anti-anaphylactic agents, Nohara *et al.* applied a series of different methods to synthesize azaxanthone derivatives, inspired by xanthone-2-carboxylic acids bearing a tetrazole group, which have proven to show oral antiallergic activity.[181,188] The authors converted chromone-3-carbonitriles **133** into 2-aminochromone-3-carbaldehydes **160** which were found to be good starting materials for the synthesis of some types of heterocycles. After the synthesis of these intermediates, some different synthetic methodologies were applied to produce different azaxanthones (Scheme 22).

The first method used was the reaction of **160** with ethyl propiolate with triethylamine (TEA) in DMF, yielding an aminoacrylate **161** (Scheme 22A), which was then converted by further heating to the desired azaxanthone **162**, in 19% yield. A similar product could be obtained by a one-step reaction, using methyl malonyl chloride (Scheme 22B), in 36% yield.[181] A different approach was the reaction of **160** with cyanoacetylene, yielding 3-cyano derivatives (**165**), in 36% yield (Scheme 22D). In this reaction, no basic catalyst was needed. The search for an alternative to this methodology, since cyanoacetylene is unstable and sublimates at low temperatures, among other undesirable properties, led to the synthesis of the same type of compound **165** in 33% yield, using α-chloroacrylonitrile with triethylamine (Scheme 22E). A second alternative to prepare **165** is the treatment of **160** with DMF and cyanoacetyl chloride, which produced the desired

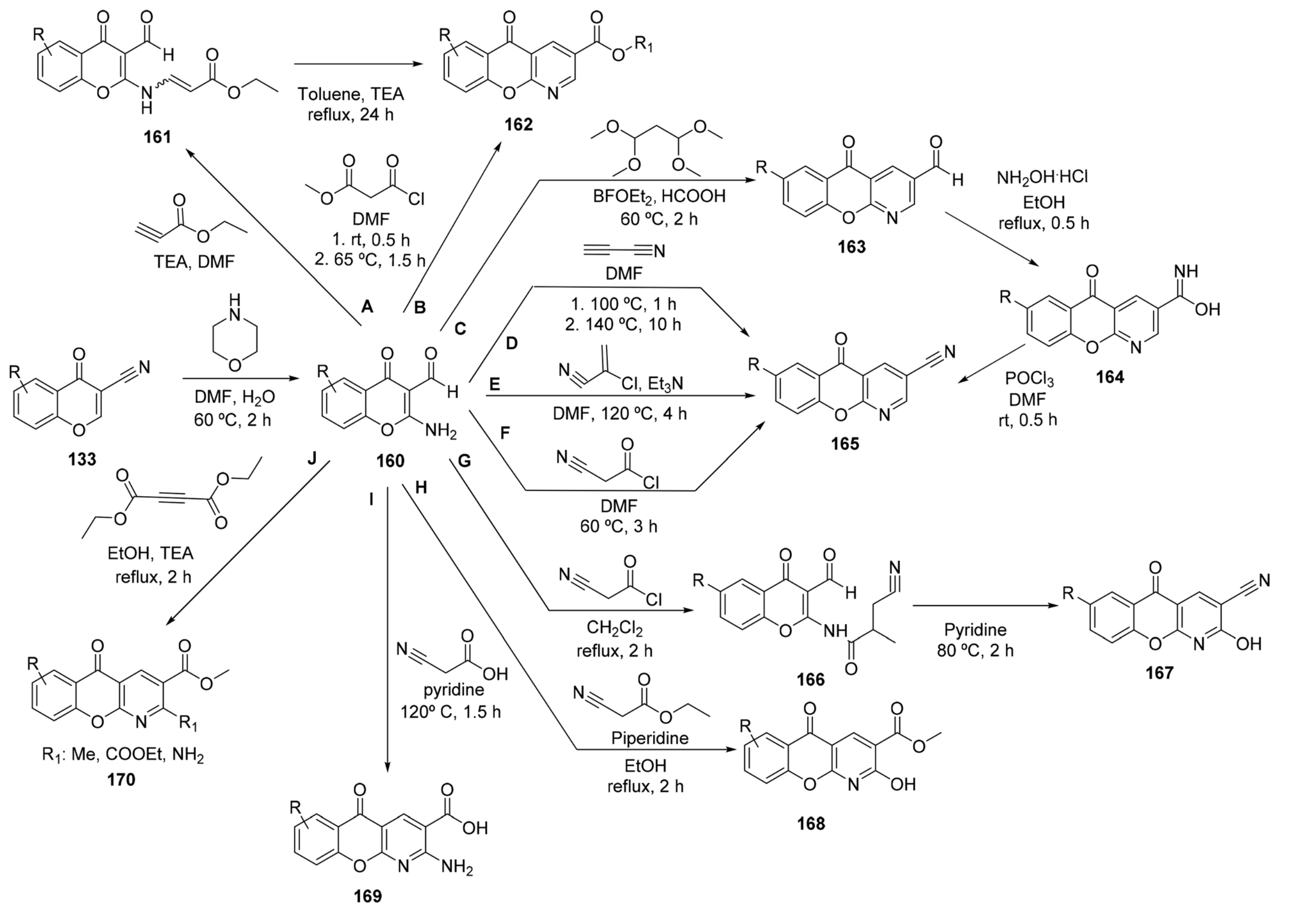


Scheme 21 Synthesis of xanthones from 2,3-disubstituted chromones.

compound in 49% yield (Scheme 22F).[181] The change of DMF for dichloromethane, in the reaction with cyanoacetyl chloride, produced an amide intermediate (**166**) (Scheme 22G), which could be converted into an azaxanthone **167** by heating with pyridine.

In this case, the azaxanthone obtained was 2-hydroxy substituted (**167**), in 22% yield.[181] The same group used another synthetic strategy towards the synthesis of azaxanthones, which was the condensation of **160** with malonaldehyde. As such, a derivative of **160** was chosen to react with malonaldehyde bis(dimethyl acetal), in the presence of formic acid in boron trifluoride etherate, affording compound **163** in 61% yield (Scheme 22C). Afterwards, an oxime (**164**) was prepared through the reaction of **163** with hydroxylamine, with 95% yield. Finally, a nitrile (**166**) was obtained by the reaction with phosphoryl chloride in DMF (Scheme 22), yielding 36% of the desired compound.[181] The same group also performed reactions where the final product would be a 2-substituted azaxanthone. The methods used ethyl cyanoacetate and piperidine (Scheme 22H, 95% yield), cyanoacetic acid and pyridine (Scheme 22I, 55%) and diethyl acetylenedicarboxylate (Scheme 22J, 91%), yielding azaxanthone derivatives **168**, **169** and **170**, respectively.[181]

5.3.5 Synthesis of azaxanthones *via* a modified Friedländer reaction. The synthesis of azaxanthones can also be achieved through modification of the Friedländer reaction. Using *o*-aminoaromatic aldehydes and unmodified ketones, Dormer *et al.* (2003) proceeded to synthesize 2-alkylsubstituted products, in a regioselective manner. The main objective was to evaluate the efficiency of several catalysts in terms of regioselectivity, conversion ratio and reaction conditions, and it was concluded that 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO) was the most effective. Slow addition of the ketone had a positive impact on regioselectivity, and reaction temperature also played a key role.[189] For the preparation of an azaxanthone using this method, 2-amino-3-formylchromone (**160**) and 2-hexanone (**171**) were chosen as the starting materials. The chromone was slowly added to a solution of the ketone, sulfuric acid, and the catalyst in ethanol. Out of all the reactions this group performed, this was the one with the lowest regioselectivity [80% 3-substituted (**172**) (79% overall): 20% 2,3,-disubstituted (**173**) (20% overall)] (Scheme 23A). Curiously, this



Scheme 22 Synthesis of azaxanthones starting from 2-aminochromone-3-carbaldehyde **160**.

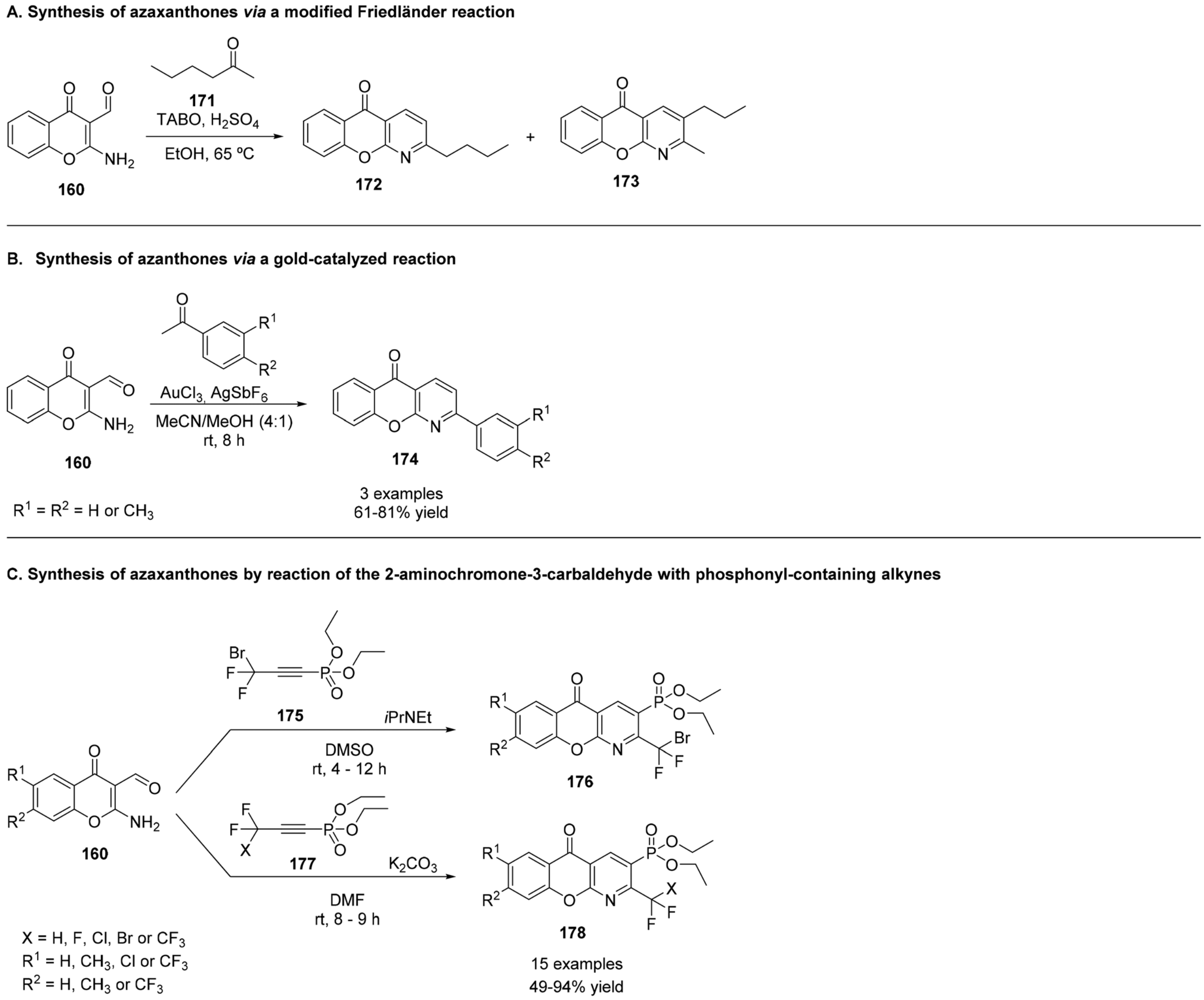
reaction did not occur under the conventional Friedländer conditions.[189]

5.3.6 Synthesis of azanthones *via* a gold-catalysed reaction. A collection of N-heterocycles, including azaxanthones, was synthesized through gold catalysed synthesis. The condensation of 2-amino-3-formylchromone **160** and acetophenone derivatives, using gold(III) chloride and silver hexafluoroantimonate(V), and a mixture of acetonitrile and methanol as solvents, gave aryl substituted azaxanthones **174** with good yield (Scheme 23B).[190]

5.3.7 Synthesis of azaxanthones by reaction of the chromone-carbaldehyde with phosphonyl-containing alkynes. The synthesis of the azaxanthone scaffold was also described by a different route in an attempt to prepare 2-difluoromethyl-azaxanth-3-ylphosphonates. Duda *et al.*[191] showed a synthetic method that led to these compounds through 2-amino-3-formylchromone (**160**) which reacted with unsymmetrical substituted electron-poor halogen-CF_2 and phosphonyl-containing alkynes **175** and **177**. The reaction occurred with DMSO as a solvent and a basic catalyst, at room temperature. It was proven that the best conditions for the synthesis of fluorine, chlorine, difluoromethyl and trifluoromethyl derivatives **176** was DMSO as the solvent and iPrNEt as the catalyst, while for derivatives **178**, the best basic catalyst was potassium carbonate and DMF was the best solvent (Scheme 23C). In the formulated hypothesis of the reaction mechanism, the base-activated 2-aminochromone-3-carbaldehydes reacts in a regioselective manner through a Michael-type addition with the carbon containing the halogen-CF_2, which is the most electrophilic. Formation of a dipolar allene, and subsequent intramolecular cyclization into the dihydropyridine derivative, leads, after dehydration, to azaxanthone. The polar solvent has utmost importance in this reaction, serving as a stabilizer and possibly interacting with the allene intermediate. An interpretation of the reaction mechanism is depicted in Scheme 23C.[191]

6 Other methodologies

Other important and conceptually different approaches, which do not belong to any of the categories described above, were also reported, manly focusing in tandem and/or rearrangement reactions. Although some of them start from readily available substrates,[192] other require complex starting materials that usually need to be prepared prior to the reaction,[193,194] but also capable of reaching unusual substituents/patterns of substitution in the xanthonic core.



Scheme 23 Synthesis of azaxanthones from 2,3-disubstituted chromones.

6.1 Synthesis of xanthones *via* decarbonylative coupling

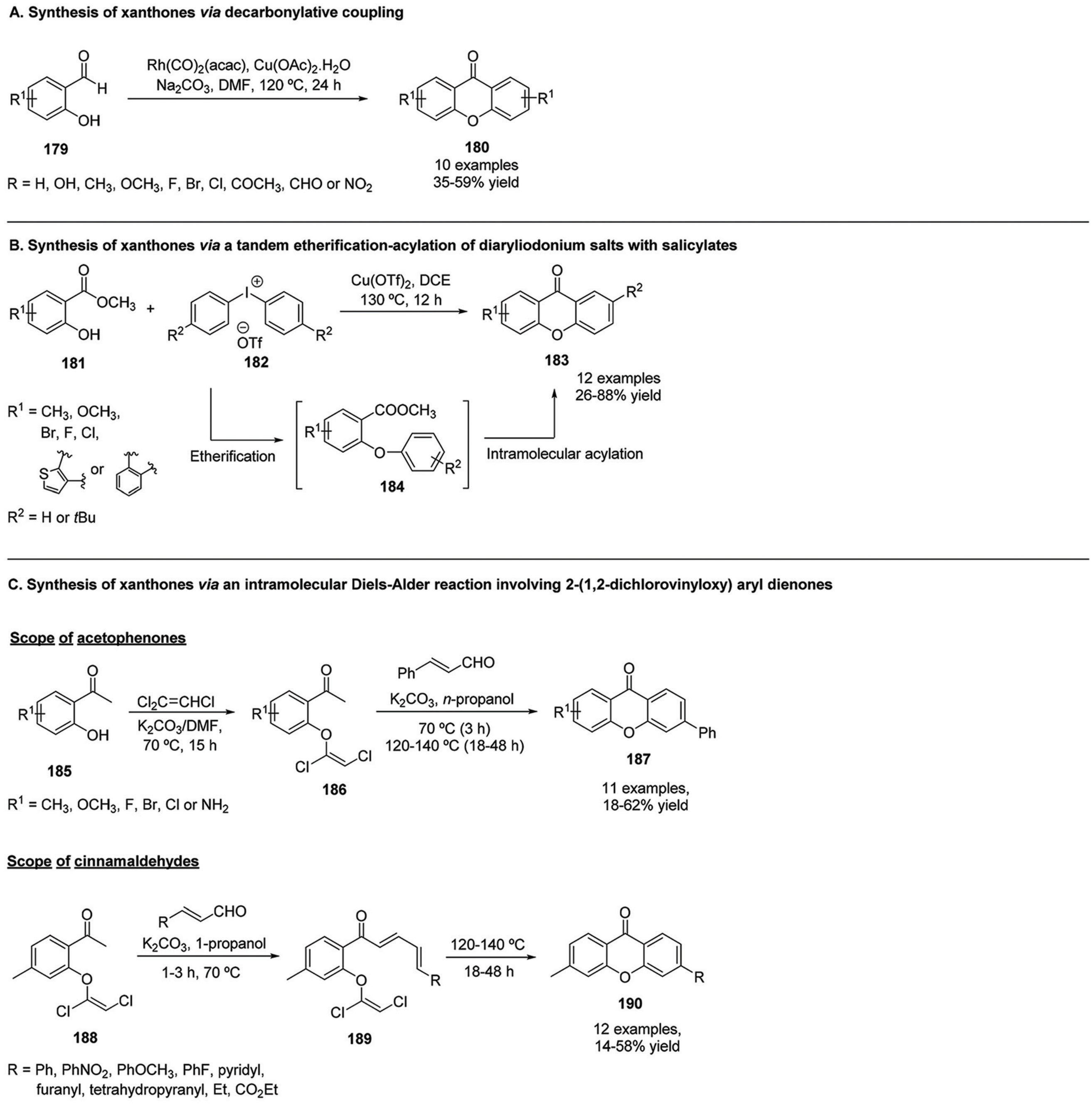
Salicylaldehydes can also be used as substrates in rhodium-catalysed reductive decarbonylative couplings to give symmetrically substituted xanthones **180** (Scheme 24A), containing formyl, bromo, chloro, fluoro, methyl, acetyl, nitro, hydroxyl, and trimethoxy groups (10 examples).[141] Interestingly, this reaction revealed to be site-selective since when 4-hydroxyisophthalaldehyde was used as a substrate, the corresponding 9-oxo-9*H*-xanthene-2,7-dicarbaldehyde was obtained, indicating the preferential reaction of the formyl group *ortho* to hydroxyl during the decarbonylative homo-coupling process.[141]

6.2 Synthesis of xanthones *via* a tandem etherification–acylation of diaryliodonium salts with salicylates

Salicylates can also be employed for the synthesis of substituted xanthones **183**, when combined with diaryliodonium salts.[195] An intermolecular etherification–acylation in the presence of $Cu(OTf)_2$ as a catalyst in dichloroethane (DCE) produced the desired xanthones in good yields (Scheme 24B). Mechanistically, the reactions are initiated by the etherification of diaryliodonium salts with salicylates, followed by an intramolecular acylation.

6.3 Synthesis of xanthones *via* an intramolecular Diels–Alder reaction involving 2-(1,2-dichlorovinyloxy) aryl dienones

An intramolecular Diels–Alder reaction where both of the pyrone and the second aromatic rings are forged in a single step was reported for the synthesis of xanthones.[192] The scope of the route to several substituted xanthones was tested by using different 2′-hydroxyacetophenones (**185**) to prepare the corresponding 1,2-dichlorovinyloxy acetophenones (**186** and **188**) that react *in situ* with cinnamaldehyde (Scheme 24C). Similarly, the scope of the reaction was also

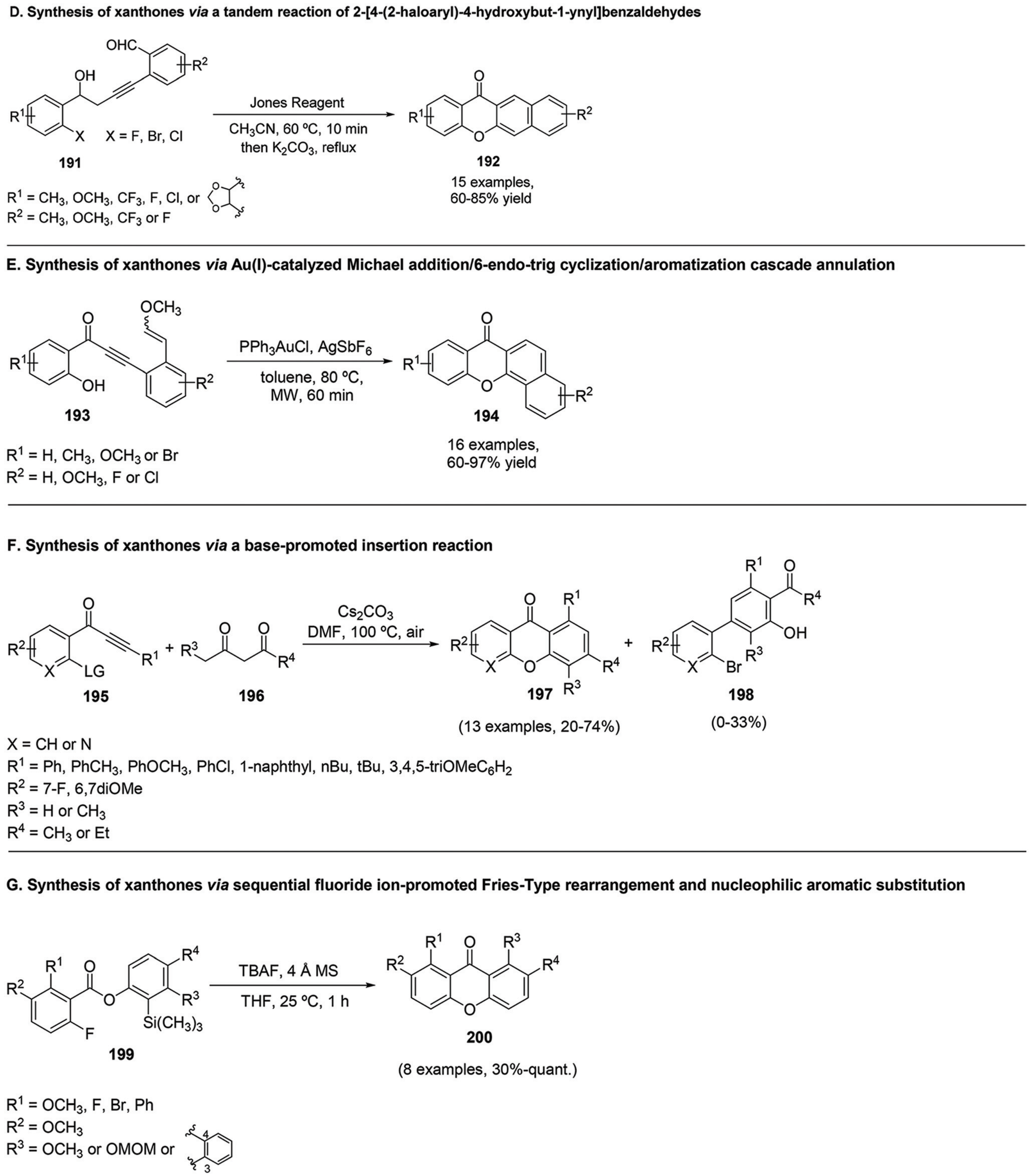


Scheme 24 Other methodologies for the synthesis of xanthones and azaxanthones.

examined using a variety of commercially available α,β-unsaturated aldehydes (Scheme 24C) with the expected xanthones **187** and **190** being obtained in modest yields (23 examples, 18–62%).[192]

6.4 Synthesis of xanthones *via* a tandem reaction of 2-[4-(2-haloaryl)-4-hydroxybut-1-ynyl]benzaldehydes

12*H*-Benzo[*b*]xanthen-12-ones **192** were synthesized using Jones reagent and K_2CO_3 promoted tandem reaction of 2-(4-(2-haloaryl)-4-hydroxubut-1-ynyl)benzaldehydes **191** (Scheme 24D).[193] The scope and limitation of this reaction were studied and it was found that in addition to a 2-bromo substituted substrate, 2-fluoro or 2-chloro derivatives could also be obtained. Due to fluoride's great inductive effect, which accelerates the rate-determining step of the nucleophilic aromatic substitution step, it was observed that fluoro substituted substrates reacted faster than bromo or chloro. However, a bromo substituted substrate was more reactive than 2-chloro since, as is well known, Br is a better leaving group than Cl. It was proposed that the overall transformation presumably proceeds through an initial tandem reaction of



Scheme 24 *(Contd)*.

191 with the formation of a 3-acyl-2-naphtol key intermediate, which should be simultaneously transformed into the corresponding phenoxide in the presence of K_2CO_3. Further intramolecular *O*-arylation occurs to give the expected 12*H*-benzo[*b*]xanthen-12-ones **192**.

6.5 Synthesis of xanthones *via* Au(I)-catalysed Michael addition/6-*endo-trig* cyclization/aromatization cascade annulation

Another strategy used for the synthesis of 7*H*-benzo[*c*]xanthen-7-ones **194** is through a Michael addition/6-*endo* cascade cyclization/aromatization, extensible to the synthesis of benzoacridones (Scheme 24E).[194] While the presence of electron-withdrawing groups on the methoxyvinyl phenyl ring led to production of the target xanthones in higher yields, when they were present in the phenol ring poor yields were obtained, regardless of the substitutions on the methoxyvinyl phenyl ring.[194] The observed outcome of the reaction could be explained by the formation of a complex with the gold catalyst, activating the 1,3-diphenylprop-2-yn-1-one which is then attacked by the hydroxyl group in a 6-*endo-dig* manner. Photodeauration of the formed intermediate and further attack of the newly formed enol ether to the electron-rich methoxyl vinyl ether gave the final xanthone after isomerization and aromatization through the release of methanol.

6.6 Synthesis of xanthones *via* a base-promoted insertion reaction

In a completely different approach, xanthones and azaxanthones were obtained through a base-promoted insertion and transition-metal-free reaction of isolated internal alkynes with β-diketone compounds (Scheme 24F).[196] Studies on the scope of the reaction revealed that different leaving groups on the acetylenic ketone **195** were well tolerated, although 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (LG = Br) produced the target xanthone **197** in the highest yield and greatest chemoselectivity. The corresponding acetyl aroyl derivative **198** was obtained as a secondary product (10% yield) of the reaction, which increased when an electron-withdrawing substituent (R^2 = 7-F) was employed.

6.7 Synthesis of xanthones *via* sequential fluoride ion-promoted Fries-type rearrangement and nucleophilic aromatic substitution

A mild and efficient reaction promoted by fluoride ions was used to prepare 1,8-disubstituted xanthones **200** from phenyl benzoate derivatives **199** (Scheme 24G).[197] The reaction proceeded *via* a Fries-type rearrangement to generate a benzophenone intermediate that immediately cyclizes into the expected xanythones due to the presence of phenoxide and fluorine moieties at the C-2 and C-2′ positions. This methodology is particularly useful for the synthesis of xanthones with steric hindrance around C-9, which are difficult to obtain through other methodologies.

6.8 Synthesis of azaxanthone-derivatives: the case of five-membered ring azaxanthones

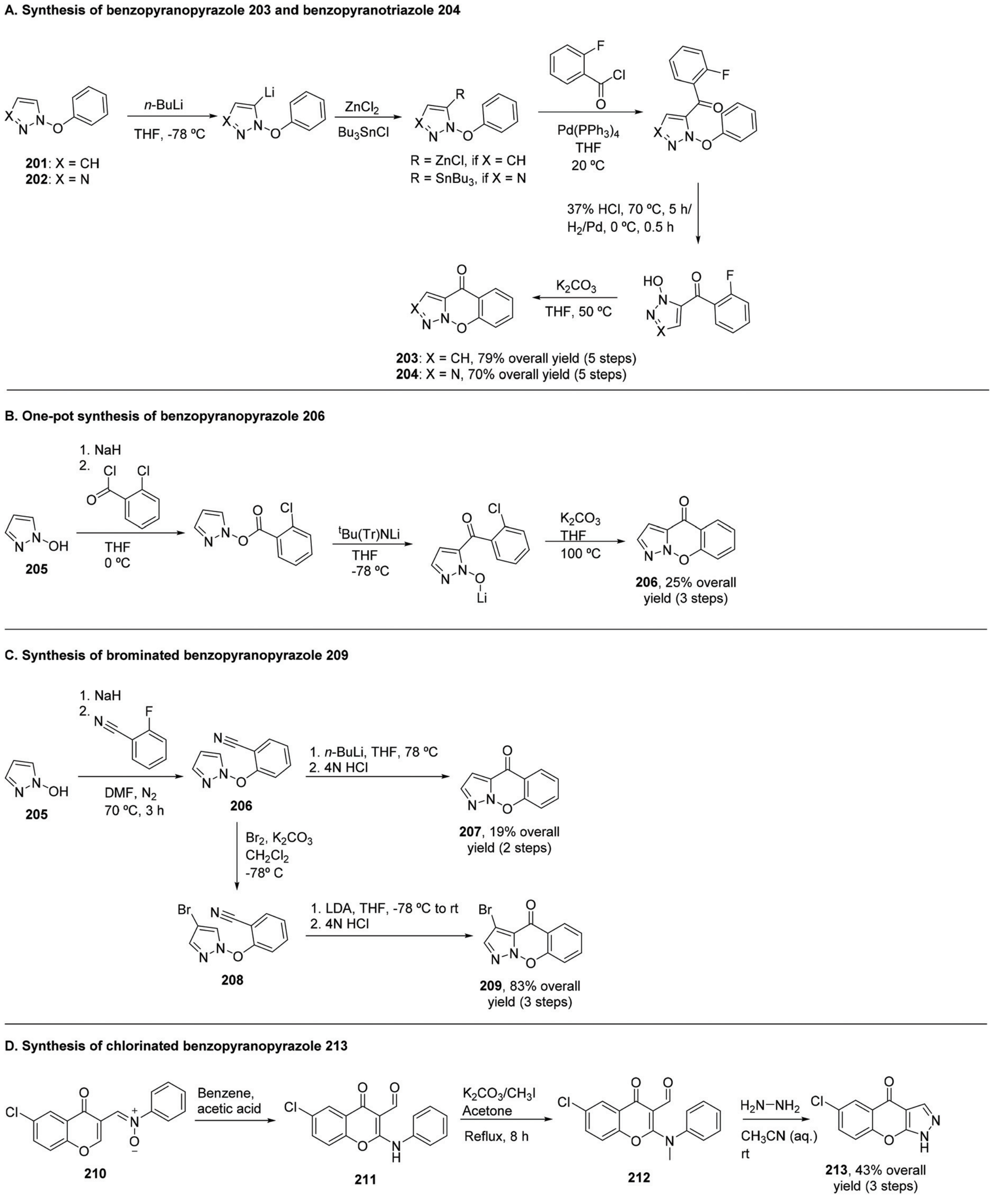
Different types of azaxanthones have been synthesized. Noteworthy for their biological activities are the five-membered ring azaxanthones. The incorporation of a pyrazole and a triazole moiety in the xanthone core can be achieved by two different methods. In the first method (Scheme 25A), an intramolecular S_NAr would be responsible for the construction of the central ring; in the second method (Scheme 25B), an anionic intramolecular ring closure takes place. Concerning the first method, 1-(benzyloxy)pyrazole (**201**) and 1-benzyloxy-1,2,3-triazole (**202**) were metalated, using butyllithium in THF, at −78 °C. The second step was slightly different for the two lithiated compounds: for the pyrazole derivative, transmetalation with zinc(II) iodide or chloride was performed, followed by cross-coupling 2-fluorobenzoyl chloride and tetrakis(triphenylphosphine)palladium(0) in THF at 20 °C. The next step was debenzylation, using hydrochloric acid.[198] On the other hand, for the triazole derivative, the transmetalation step occurred with tributylstannane, and the debenzylation with H_2/Pd.[199] The ring closure proceeded under mild conditions, using potassium carbonate in DMF, at 50 °C.[200] The overall yield was 79% for the benzopyranopyrazole (**203**) and 70% for the benzopyranotriazole (**204**). Scheme 25A shows the reactions used to obtain this kind of azaxanthone.

A one-pot approach was also achieved, which represented a faster way of obtaining a pyrazol-containing azaxanthone, albeit with a more modest yield of 25% (Scheme 25B). In this reaction, 1-hydroxypyroxazol (**205**) was used as the starting material, and was dissolved in THF, at 0 °C, under a nitrogen atmosphere, and sodium hydride was added. Afterwards, 2-chlorobenzoyl chloride was added and, after the reaction vessel was cooled to −78 °C, lithium *t*-butyltritylamide was added. Then, the mixture was allowed to heat to room temperature and potassium carbonate was added, followed by heating to 100 °C for 10 hours, yielding the desired azaxanthone (**206**) (Scheme 25B).[200]

The second route was aimed to construct the *O*-aryl bond before closing the ring. As such, efforts were placed towards the synthesis of a cyano diaryl-ether (**206**), since the cyano group constitutes an activating group in nucleophilic aromatic substitution (Scheme 25C). 1-Hydroxypyroxazol (**205**) reacted with 2-fluorobenzonitrile, in the presence of sodium hydride, in DMF, under a nitrogen atmosphere, for three hours, at 70 °C. *n*-Buthyllithium was used for the lithiation, in THF, at −78 °C. Addition of hydrochloric acid led to the desired azaxanthone **207**, with a low yield of approximately 20%. Studies demonstrated that the 4-bromo derivative of the cyano precursor (**208**) would give the desired azaxanthone **209** in a more satisfactory 83% overall yield (3 steps), only changing the lithiation reagent to LDA, in order to avoid halogen-metal exchange (Scheme 25C).[200]

Another method towards obtaining five membered ring azaxanthones was proposed by Singh *et al.*[201] Starting from a nitrone **210**, 2-anilino-6-chloro-3-formylchromone (**211**) was formed in dry benzene, with a few drops of acetic acid (Scheme 25D). A reaction with methyl-iodide in the presence of potassium carbonate in acetone yielded 6-chloro-2-(*N*-methylanilino)-3-formylchromone (**212**), which upon reaction with hydrazine hydrate in aqueous acetonitrile overnight afforded the azaxanthone **213** (Scheme 25D) in 43% overall yield.

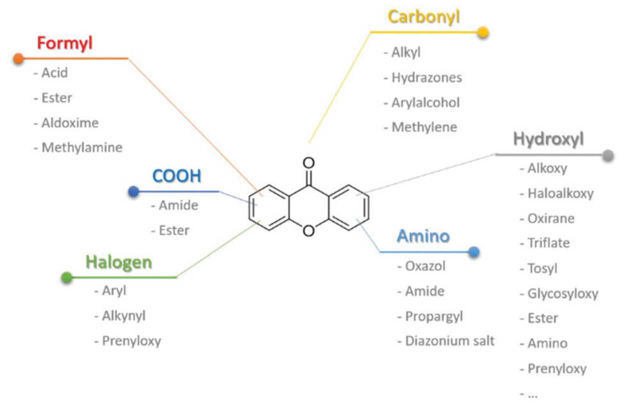
Besides the synthesis of bioactive azaxanthones, the synthesis of thioazaxanthones and their use as photosensitizers[15,202] have been reported as well as the synthesis of more complex pyranoazaxanthones, fused ring azaxanthones[203–205] and others.[89,206–218]



Scheme 25 Other methodologies for the synthesis of xanthones.

7 Diversification on the xanthone core

Hydroxyl groups are undoubtedly one of the most versatile functional groups when it comes to structural modifications (Scheme 26). A myriad of examples have been described in the literature, including the reaction with alkyl halides for the transformation into alkoxy,[43,59,69,219–223] haloalkoxy,[18,51,69,99,224] methyl alkyl- or aryl-piperazine moieties,[225] epoxypropanoxy[65,103,220–222] oxirane[221], oxypropanolamines,[103] benzenesulfonamides,[226] and propargyloxy.[45,52,54,63,106,118,173,227,228] When reacted with other compounds that are not alkyl halides, several other functional-



Scheme 26 Most common molecular diversifications on substituted xanthones.

ities can be achieved like alkoxy,[19,23,24,33,97] which in certain situations can be converted into chlorosulfonyl[24] or amine,[33] ethylenedioxy,[100] and allyl.[39,115,138] Other transformations include the introduction of glycosyl,[55,110,132,135,229,230] ester,[17,62,227] amino,[151] and even prenyl[23,39,40,45,46,49,50,52,53,97,98,111–114,117,130,133,221,231–233] moieties, the latter being further used for the synthesis of caged xanthones[39,49,105,138,234] or pyranoxanthones.[40,45,46] Ultimately, hydroxyl groups can be converted into triflates which provide easy access towards amines,[227,235] imines,[116,140,235] aryl,[119,236] and alkyl xanthones,[155] or even converted into tosyl groups for further transformations[110] for the introduction of amines. Aminoxanthones can be obtained through reduction of the nitro group.[54,60,108,227,237,238] Further transformation of the amino moiety can be used for the synthesis of oxazol,[60] amide,[108,237–239] and propargyl[54] xanthone derivatives or even transformed into hydroxyl, chloro, iodo or arylxanthones *via* diazonium salts.[219] Carboxyxanthone derivatives can be coupled with amines to obtain the corresponding amides[47,151] or esters.[240] Although the methyl group is usually not considered a highly versatile group, after a simple bromination[66,71,219,241] it is possible to obtain several other functionalities. For example, imidazolylmethyl,[219] methylhydroxy,[66] methylamine[241] or formyl,[66,71] the latter being further transformed into methylamine,[33,71] acid,[240] ester[240] and aldoxime[240] moieties. The presence of a halogen substituent at the xanthone core also provides an opportunity for further transformations. Recent examples include iodo[137] or bromo[197] to aryl *via* arylboronic acids, or bromo to alkynyl xanthones *via* Sonogashira coupling.[197] On the other hand fluoro can undergo S_NAr reactions with pyrrolidine and sodium ethoxide[197] or installation of the isoprenyl moiety *via* isoprenyl Grignard reagent.[231]

8 Conclusions

The importance of xanthones and azaxanthones in medicinal chemistry led to the employment of advanced synthetic methodologies in these heterocyclic scaffolds. For obtaining xanthones and azaxanthones three starting points are generally used: the benzophenone, the diaryl ether or the chromone.

The benzophenone route consists of a multi-step approach using a benzoic or nicotinic acid derivative, followed by a cyclization, finally leading to the xanthone scaffold. The diaryl ether route focuses on a classic Ullmann condensation between an aryl halide and a phenol derivative. The cyclisation can be achieved by a wide range of methodologies, being also a multi-step approach. On the other hand, the chromone route is usually a one-step strategy. These reactions are not exclusive to the (aza)xanthone scaffold, being transversal to the synthesis of many heterocycles, such as flavones, coumarins, acridines, among others which expand the scope of the reaction conditions presented herein.

It can also be observed that many approaches are being revisited and recent advances made with the aim of developing greener methods, such as one-pot reactions, MAOS, solvent- and metal-free strategies. Nanocatalysts represent a significant advancement in catalytic activity over conventional catalytic methods in several synthetic approaches with a diversity of catalysts being employed, such as palladium and magnetically separable nano-$CuFe_2O_4$ allowing also high throughputs in purification procedures.

New reagents for transition-metal systems are emerging and include pyridylmagnesium reagents and *N*-heterocyclic carbenes with unique reactivities that have been used in a broad range of organometallic transformations and are expected to increase in the following years. Also, metal-free conditions are being applied such as metal-free variants of the intramolecular Friedel–Crafts acylation, with quaternary ammonium salts like tetrabutylammonium bromide (TBAB)-promoted intramolecular annulation in aqueous medium standing out. Concerning atom economy, one-pot approaches rule with multicomponent and domino/tandem reactions being often applied in the cyclization reactions of (aza) xanthones. Solvent-free conditions and more efficient catalysts are being disclosed such as indium triflate, ytterbium(III) trifluoromethansulfonate, Cu(0)/Selectfluor system, dichloro(*p*-cymene)ruthenium(II), and also in palladium catalysed carbonylations/C–H activation reactions. Recent trends are the radical cyclization *via* photoredox catalysis using photosensitizers and the cross-dehydrogenative reaction that involves a few steps and can be extended to a wide scope of derivatives.

This review also shows that the xanthone scaffold still gathers a lot of attention not only from a synthetic point of view but due to the diversity of bioactive derivatives being disclosed, the case-studies of this study. New biological applications are being proposed for xanthones beyond their pharmacological properties with relevance for chemical biology as sensitizing chromophores. Therefore, it is useful to know the vast array of approaches being used, as they can become a valuable toolbox in the search of novel bioactive heterocycles, emphasizing the importance of this privileged scaffold. Moreover, the site-selective late-stage functionalization approaches highlighted herein can guide medicinal chemists in the lead optimization not only of (aza)xanthones, but also of isosters like thioxanthones, acridones, cromones, flavones, among others. This review can help guide medicinal chemists working with heterocycles by providing chemical tools and reaction conditions to both target and diversity-oriented synthetic approaches.

Conflicts of interest

There are no conflicts to declare.

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