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Review

Azulene, Reactivity, and Scientific Interest Inversely Proportional to Ring Size; Part 1: The Five-Membered Ring

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Abstract: The lack of azulene symmetry with respect to the axis perpendicular to a molecule creates an asymmetry of the electronic system, increasing the charge density of the five-atom ring and favoring its electrophilic substitutions. The increased reactivity of this ring has contributed to ongoing interest about the syntheses in which it is involved. The aim of this review is to present briefly and mainly in the form of reaction schemes the behavior of this system. After a short chapter that includes the research until 1984, subsequent research is presented as generally accepted chapters and subchapters to describe the behavior of the azulene system: metal free catalyst reactions; reactions catalyzed by metals; various azulene five-ring substitutions. The author insists on reaction yields, and in some cases considers it useful to present the proposed reaction mechanisms.

Keywords: azulene; five-ring reactivity; cross-coupling

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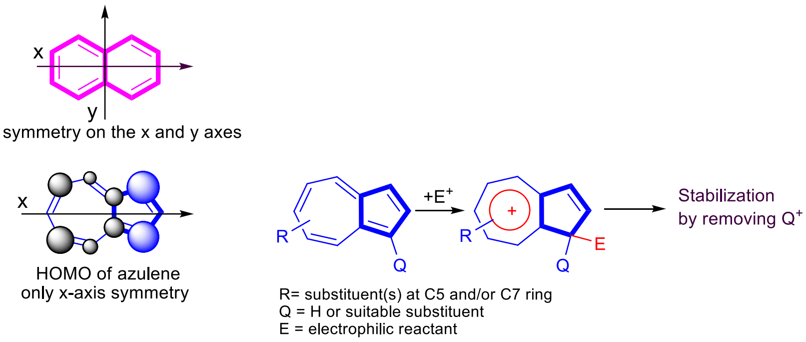
1. Introduction

Used as a dye since the 16th century and synthesized by Lavoslav Ružička in 1937, azulene is still of great interest for researchers. The structure and physicochemical properties of azulene compounds contribute to this, as well as a series of their uses in various fields of activity. Therefore, it is not surprising that many scientific papers have appeared about azulenes: communications, articles, reviews, patents and chapters of monographs. Some of them refer to the structure and chemistry of azulene and others to the uses of azulene compounds. Thus, a large number of azulene derivatives have real or potential uses as anti-inflammatory [**Error! Reference source not found.**], antitumor [**Error! Reference source not found.**], and bioimaging material [**Error! Reference source not found.**] as dyes [**Error! Reference source not found.,Error! Reference source not found.**], for solar cells [6–8], organic semiconductors, or modified electrode agents [**Error! Reference source not found.**].

Much richer is the literature that deals with the chemistry of the azulenes, and any attempt to exhaust this subject would far exceed the volume of a book. A substantial chapter on the research in this field conducted until 1984 was published by Zeller in the Houben–Weyl encyclopedia [**Error! Reference source not found.**]. That chapter included the synthesis of each of the two azulene rings as well as their reactions. After this contribution and until now, several azulene-containing reviews have appeared, and most of them are mentioned below.

The present review is to some extent a continuation of a review recently published by the author [**Error! Reference source not found.**]. The lack of azulene symmetry with respect to the axis perpendicular to a molecule creates an asymmetry of the electronic system, increasing the charge density at the five-atom ring compared to the seven-atom ring. This permanent displacement has as a consequence an increase in the nucleophilic reactivity of azulene compared to naphthalene, with symmetry towards both x and y axes (Scheme 1). The highest negative charge density is located at C1 and C3 from

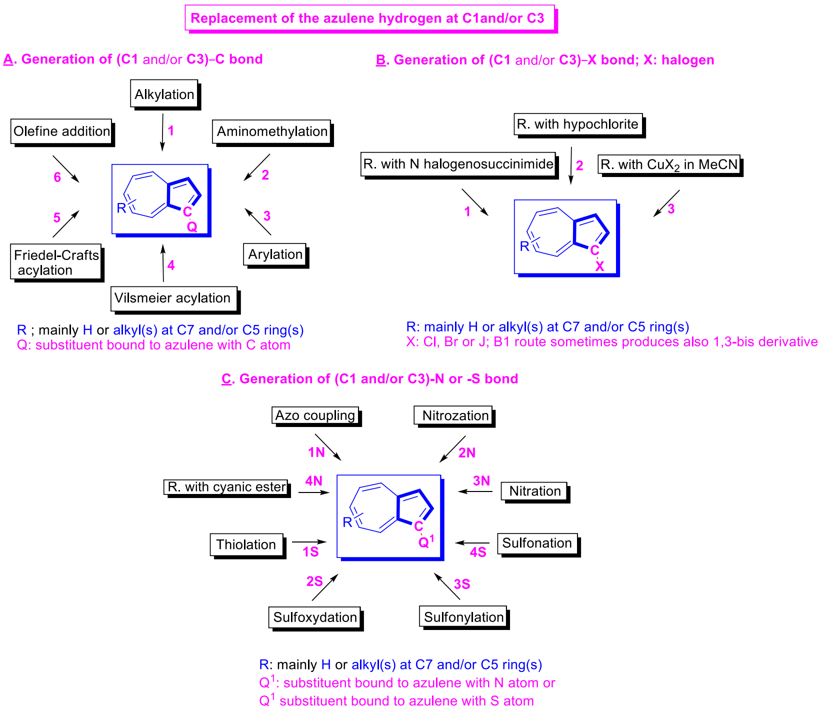
HOMO calculations [**Error! Reference source not found.**,**Error! Reference source not found.**], and the molecular symmetry of azulene framework with respect to the x-axis makes identical the behavior of these positions [11] (Scheme 1). The involvement of the seven-membered ring as a tropylium ion in the stabilization of substitution intermediates, as shown in Scheme 1, favors supplementary electrophilic azulene substitution. Nucleophilic and radical substitution at azulenes is less common and is encountered especially at the seventh ring and only seldom at the fifth ring. Because of the interest in the study of five-ring chemistry, which was much more intense compared to that for seven-ring chemistry, the behavior of the first ring is analyzed in this review, that of the seven-atom ring being in progress.



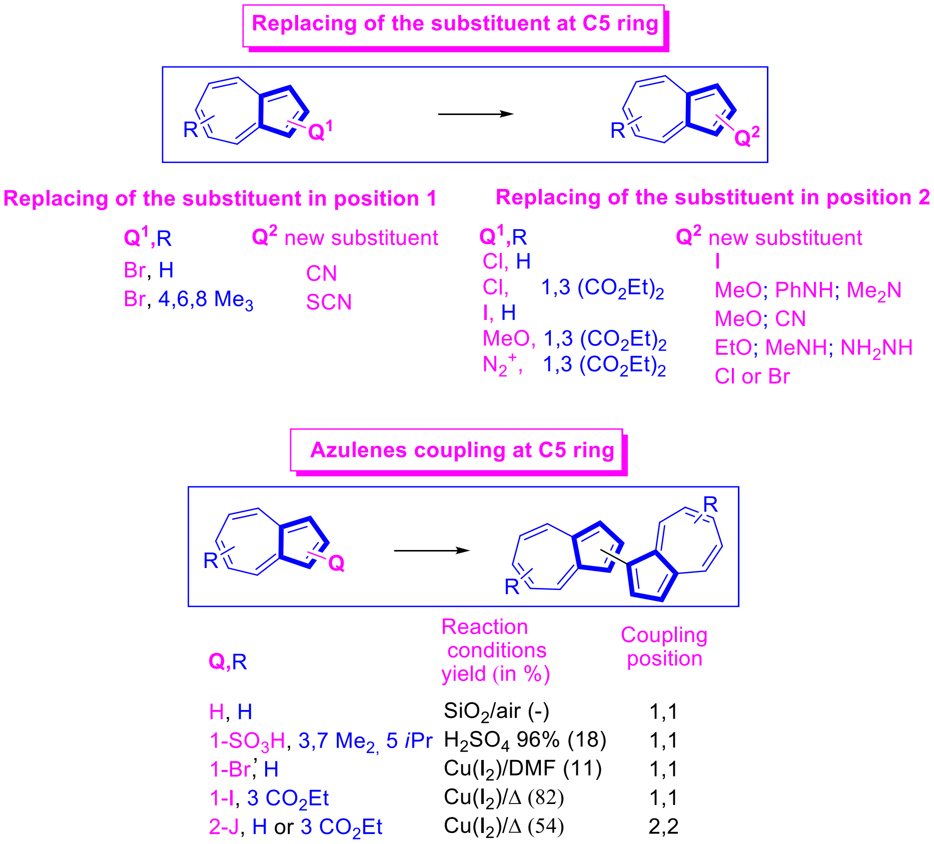
Scheme 1. HOMO of azulene and its electrophile substitution.

The presentation of the material is a little different from the general organization found in other reviews, being based mostly on reaction Schemes in which the reaction conditions and the yields in the products are given. It is assumed that this will facilitate the quick finding out of some concise information on a synthesis. Of course, other elements related to the reaction are also detailed, and sometimes the reaction mechanisms are discussed.

It is useful to begin with the very summary presentation of the material proposed in Zeller's review about the behavior of five-atom rings. Besides the historic interest, some of the reported procedures continue to be used today in the synthesis of azulene compounds. Therefore, in Schemes 2 and 3, some particular aspects resulting from Zeller's review, accompanied by brief comments about them, are briefly highlighted.



Scheme 2. Replacement of hydrogen at the five azulene ring.



Q^1,R	Q^2 new substituent
Br, H	CN
Br, 4,6,8 Me_3	SCN

Q^1,R	Q^2 new substituent
Cl, H	I
Cl, 1,3 $(CO_2Et)_2$	MeO; PhNH; Me_2N
I, H	MeO; CN
MeO, 1,3 $(CO_2Et)_2$	EtO; MeNH; NH_2NH
N_2^+, 1,3 $(CO_2Et)_2$	Cl or Br

Q,R	Reaction conditions yield (in %)	Coupling position
H, H	SiO_2/air (-)	1,1
1-SO_3H, 3,7 Me_2, 5 *i*Pr	H_2SO_4 96% (18)	1,1
1-Br, H	$Cu(I_2)$/DMF (11)	1,1
1-I, 3 CO_2Et	$Cu(I_2)/\Delta$ (82)	1,1
2-J, H or 3 CO_2Et	$Cu(I_2)/\Delta$ (54)	2,2

Scheme 3. The replacing of the substituent from position 2 and the azulenes coupling.

Scheme 2 shows the binding of azulene to carbon, halogen, nitrogen or sulfur atoms of the substituents (routes A, B and C, respectively). Some procedures described the generation of the electrophilic agent in the presence of a catalyst (A1, A2, A5), while compounds with efficient electrophilic activity, such as picryl chloride (A3) or electron-rich alkenes (A6), operate without the intervention of a condensing agent. Vilsmeier synthesis (A4) for formylation or acylation of azulenes by the reaction of dialkylacylamides in the presence of $POCl_3$ is still frequently used to obtain azulene compounds. The sensitivity of azulene compounds to halogens eliminates direct halogenation processes. Instead, halogenosuccinimide (NXS) is frequently used as halogen-substituent agent for hydrogen (B1). Scheme 2 shows also the bond generation between azulene and nitrogen and sulfur atoms (C). It should be noted that diazonium coupling (C1) continues to be a widely used procedure for the generation of azo derivatives of azulene with multiple technical purposes.

The second series of substitutions on the azulene five ring, described by Zeller, refers to the reaction of preexisting substituents (Scheme 3). As previously seen, the substitution at positions 1 and 3 is carried out relatively easily in an electrophilic way, and due to the lower electron density at position 2, it is expected that the substitution at this position will occur with more difficulty and mainly by a nucleophilic mechanism [**Error! Reference source not found.**]. Some examples of electrophile attack at this position are however known. Thus, in order to improve the electrophilicity of this position, the presence in positions 1 and 3 of electron acceptors as CO_2H, CO_2Et or CN is favorable, and thus halogens, methoxy or diazo groups at position 2 could be replaced. In Scheme 3 are also introduced examples of azulene couplings with substituent elimination in different reaction conditions, as mentioned by Zeller. As can be seen, the reported coupling yields are low, though somewhat better in the presence of the CO_2R as substituent.

Most of Zeller's early described procedures refer to obtaining azulenes substituted mainly with atoms or relatively simple functions. Furthermore, severe reaction conditions and/or modest obtained yields limit the use of these processes in many cases.

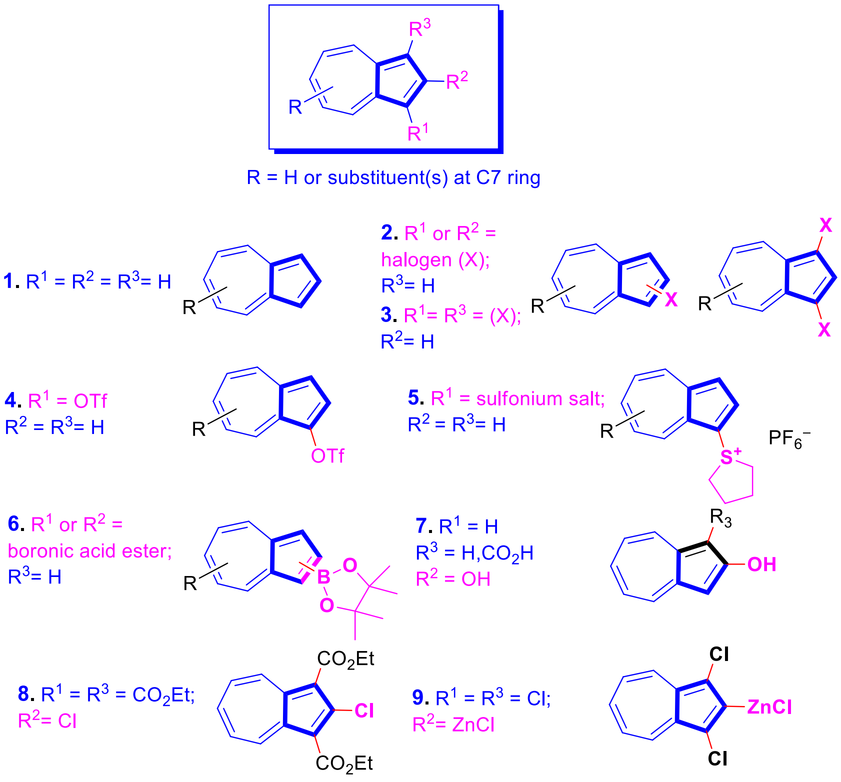
The ongoing increase in interest in the chemistry and utilization of azulene compounds is reflected by the continuous accumulation of information on this subject. As a result, the literature concerning azulene compounds has been greatly enriched with articles and comprehensive reviews. Soji and Ito group contributed mainly to the dissemination of information on the synthesis of heteroaryl-substituted azulenes. The overview about the preparation of functionalized azulenes for electrochromic applications presented by the authors in 2011 [**Error! Reference source not found.**] was followed by reviews from 2018 [16] and 2020 [17], which deal with the synthesis of heterocycle-substituted and fused azulenes, starting with the construction of the two rings of the azulene system or with azulene substitution. In a review on the activation of C-H bond of the five-membered azulene ring by metals [18], Shi and coworkers showed the functionalization of this ring by a series of substitution reactions. The paper of Zhuang et al. [12] presents the synthesis of azulene-based aromatic compounds for optoelectronic and energy applications. Razus et al. recently published a number of reviews on the obtaining of azulenes [11,19–21], Elhawy's article from 2021 discussed the synthesis of azulene derivatives through Pd-catalyzed coupling techniques [22] and Gao condensed information about the applications of azulene-based π-functional materials [23]. From this, it follows that most of these papers were directed towards particular and well-defined targets, for example, certain classes of compounds, synthesis routes, technical uses, etc.

This review selected and organized as much as possible the disseminated information about the very interesting chemical behavior of the five-membered azulene ring. In the following, it was preferred to cite the original materials and not the reviews, so that the reader can quickly access the desired material. From the widely reported results were selected only those considered more interesting or recently published, taking into account some structural features of the starting azulenes and the particularities of the synthesis routes. Therefore, this work is addressed especially to those who want a brief overview of this field or to beginners in azulene chemistry.

2. Starting Azulenyl Reagents

Before going through reactions in which the five-atom azulene ring is involved, some living groups, more often encountered in syntheses, are depicted in Scheme 4. Of course, the unsubstituted five ring of azulenes is frequently chosen in substitutions of the hydrogen atom (entry 1).

The halogenated azulenes are used less often because, as already mentioned, the halogenation (mainly with NXS; entry 2 and 3) produces a mixture of mono- and bis-halogenated derivatives. Other starting azulenes, for example, the triflates (entry 4 in Scheme 3), are unstable and require specific reaction conditions. Several examples of living-groups at position 2 that will be used for other starting compounds substituted in this position are also shown in the Scheme. All these compounds together with other raw materials are discussed in more detail during this review.



Scheme 4. Leaving groups (or atoms) of azulenyl reagents.

3. Reactions of Azulene Five Ring

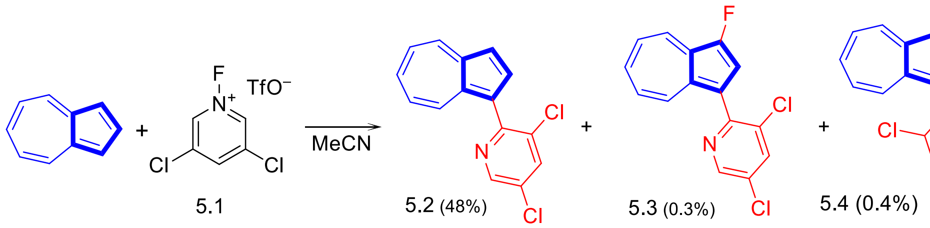
Along with other possible classifications for the azulene five-ring substitutions, these reactions can be also divided into uncatalyzed and catalyzed. As it appears after Zeller's report and to some extent in recent research, the use of the uncatalyzed route was quite rarely encountered. The results communicated lately show a focus on the reactions catalyzed by metallic compounds, which generally take place in milder conditions and with higher yields than those in which they are not present. In addition, a number of the proposed procedures lead to valuable products whose synthesis is not possible by other routes. Therefore, only several examples from the series of reactions without a catalyst will be treated first, followed by a more consistent chapter dealing with metal-catalyzed reactions.

3.1. Metal-Free Catalyst Reactions

The reactions that are the subject of this chapter are divided into electrophilic and nucleophilic substitutions—SEAz and SNAz. Some other reaction routes are also briefly analyzed. Within this division, attention was paid to the behavior of the positions belonging to the five-azulene ring.

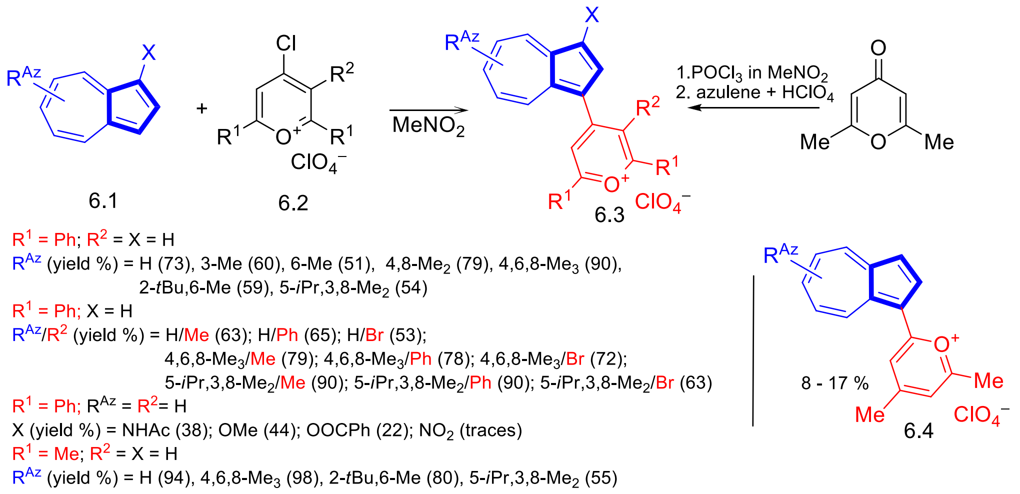
3.1.1. Azulene Electrophile Substitution, SEAz

The syntheses with which the chapter begins, start from two strong electrophiles, salts of heteroaromatic compounds. The first synthesis (Scheme 5) [24], somewhat older, uses a pyridinium salt, **5.1**. Uena et al. intended to fluorinate azulene with this salt, known as a fluorination agent, but instead of halogenation, an electrophilic substitution took place with the formation of compound **5.2** as the major product.



Scheme 5. Electrophile substitution of azulene with pyridinium salt.

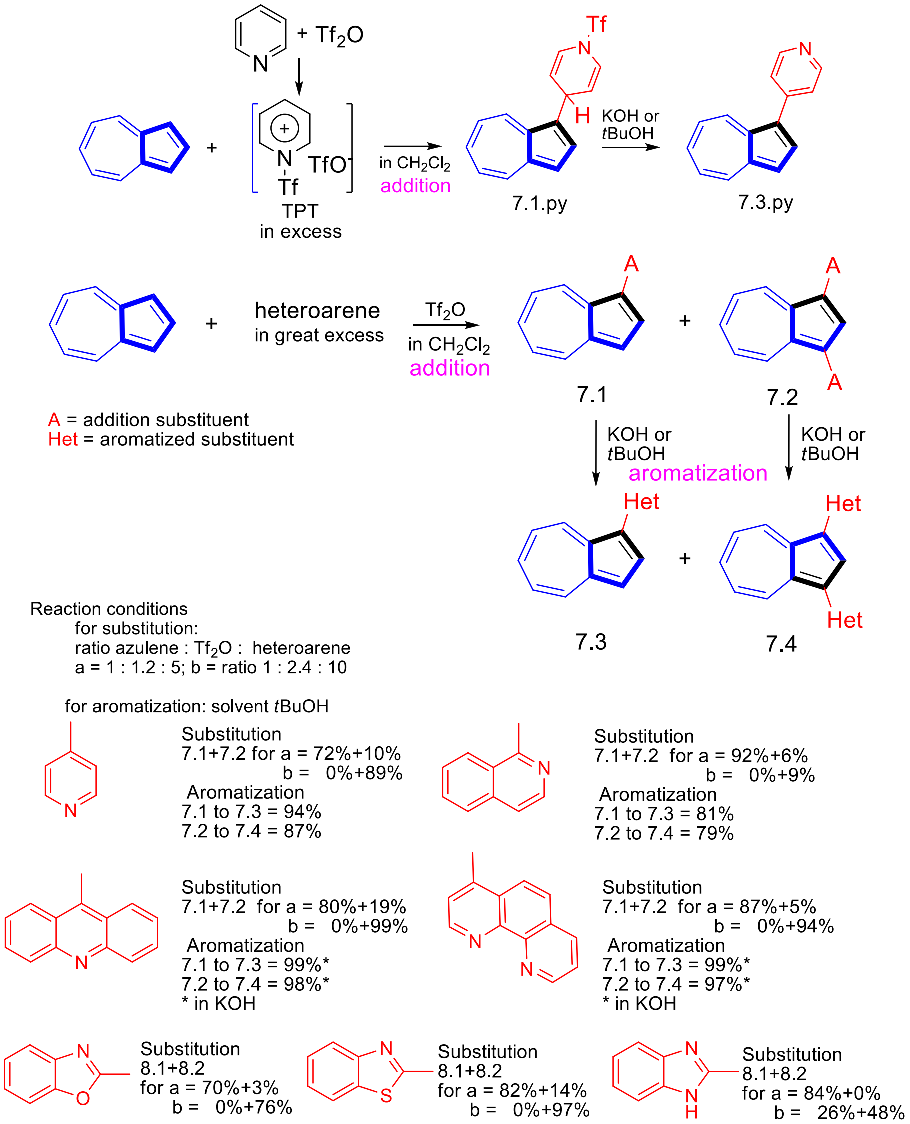
Starting from pyrylium salts, **6.2**, and azulenes, **6.1**, with different substituents, Razus et al. [25] obtained a rich series of pyrylium salts substituted with azulene, **6.3** (Scheme 6). The activation of the substitution due to the positive charge of the heterocyclic ring is noteworthy. It is also worth noting that the salt with azulene substituted in position 2 of the pyrylium system, **6.4**, was prepared in a similar way. The pyrylium salts **6.3** were transformed in the corresponding pyridines [26,27].



R^1 = Ph; R^2 = X = H
R^{Az} (yield %) = H (73), 3-Me (60), 6-Me (51), 4,8-Me_2 (79), 4,6,8-Me_3 (90), 2-*t*Bu,6-Me (59), 5-*i*Pr,3,8-Me_2 (54)
R^1 = Ph; X = H
R^{Az}/R^2 (yield %) = H/Me (63); H/Ph (65); H/Br (53); 4,6,8-Me_3/Me (79); 4,6,8-Me_3/Ph (78); 4,6,8-Me_3/Br (72); 5-*i*Pr,3,8-Me_2/Me (90); 5-*i*Pr,3,8-Me_2/Ph (90); 5-*i*Pr,3,8-Me_2/Br (63)
R^1 = Ph; R^{Az} = R^2= H
X (yield %) = NHAc (38); OMe (44); OOCPh (22); NO_2 (traces)
R^1 = Me; R^2 = X = H
R^{Az} (yield %) = H (94), 4,6,8-Me_3 (98), 2-*t*Bu,6-Me (80), 5-*i*Pr,3,8-Me_2 (55)

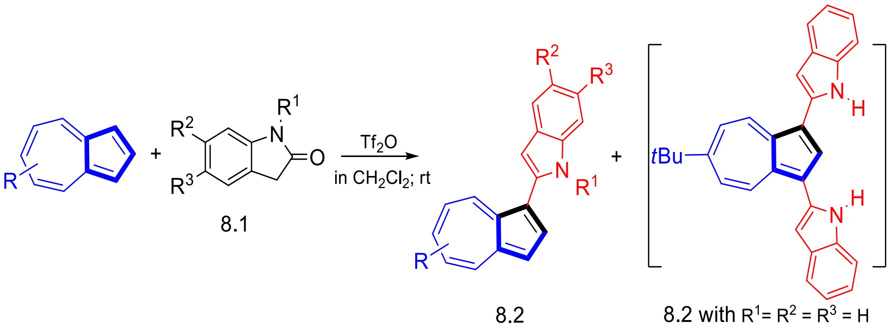
Scheme 6. Electrophile substitution of azulene with pyrylium salt.

The obtaining of azulenes substituted in position 1 (and 3) with pyridine was reported in articles published by Soji, Ito, Morita and all. With the help of triflic anhydride (Tf_2O), pyridine was transformed into a strong electrophile, trifluoromethanesulfonyl pyridiniumtrifluoromethane sulfonate (TPT), depicted in Scheme 7 [28]. The nucleophilic attack of azulene can take place in position 2 of the pyridinium salt with the opening of the pyridine ring or in position 4 in a large excess of TPT with the obtaining of additional compound **7.1.py**. The aromatization that followed takes place in the presence of a base and gives **7.3.py**. The described procedure was extended to a large number of heteroaromatics (Scheme 7) [**Error! Reference source not found.**]. Along with the disubstituted product, **7.4**, the monosubstituted one, **7.3**, is also obtained. As seen in Scheme 7, the ratio between the products is largely dependent on the ratio of the participants in the reaction.



Scheme 7. SEAz at position 1 (and 3).

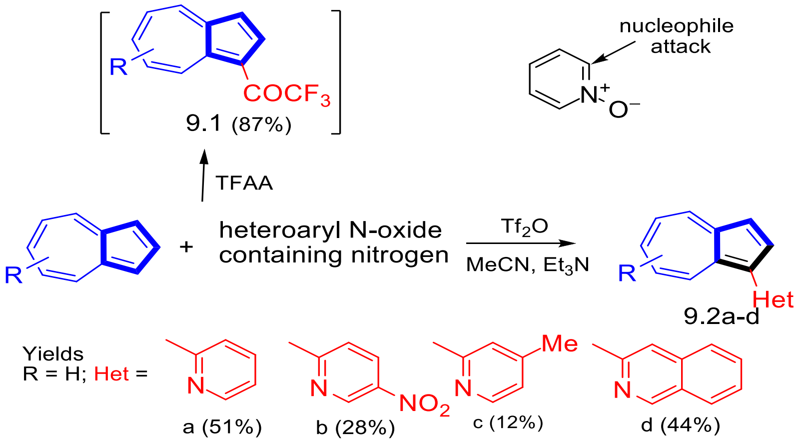
Triflic anhydride was also reported as activating reagent in the Vilsmeier–Haack-type arylation depicted in Scheme 8 for the synthesis of 1-(indol-2-yl)azulenes, **8.2** [**Error! Reference source not found.**].



Compound 8.2; Yields (%)
R = R^1 = H; R^2 = H; R^3 = Cl (91); R^2 = Cl; R^3 = H (89)
R = R^2 = R^3 = H; R^1 = Ph (27)
R^1 = R^2 = R^3 = H; R = 1-CO_2Me (71); 6-CO_2Me (45);1-Ph (88); 2-Ph (82);
8-*t*Bu (64); 1,6-*t*Bu_2 (47); 1-SMe-6-*t*Bu (43); 1-CO_2Me-2-Ph (65)

Scheme 8. Synthesis of 1-(indol-2-yl)azulenes by Vilsmeier–Haack arylation.

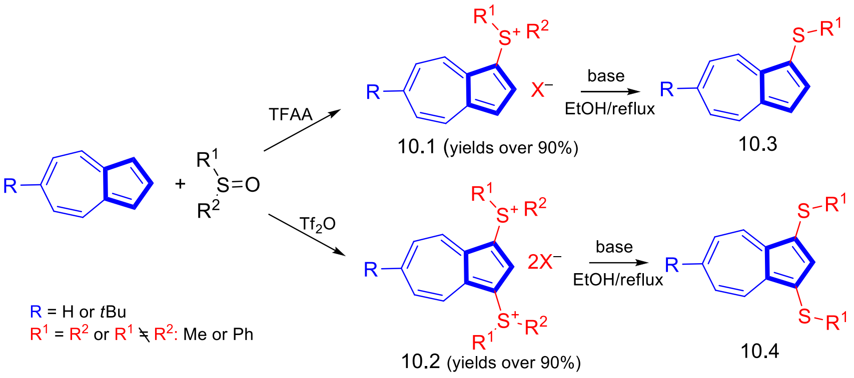
Reissert–Henze functionalization of N-containing heterocycles, depicted in Scheme 9, is based on activation with Tf_2O of the starting heteroaryl [**Error! Reference source not found.**]. Whereas trifluoroacetic anhydride (TFAA) only gives the substitution product **9.1**, the compounds of **9.2** result after substitution and reaction with NEt_3 in MeCN.



Yields
Het = 2-pyridyl; R = 2-*t*Bu (60%), 6-*t*Bu (22%), 3,7-Me_2-5-*i*Pr (30%), 6-Me_2N (55%)

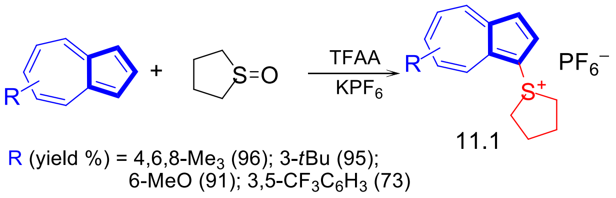
Scheme 9. Reissert–Henze reaction of azulenes with N-containing heteroaryl N-oxides.

The difference in activation with Tf_2O and that with TFAA is also illustrated in Scheme 10. The monosubstituted compound **10.1** was formed after attack on sulfoxide in the presence of TFAA, whereas compound **10.2** with position 1 and also 2 occupied resulted with Tf_2O [**Error! Reference source not found.**]. The subsequent nucleophilic substitution (S_N2) at the methyl group on the sulfonium ions **10.1** and **10.2** with 1-azulenyl sulfide, acting as a leaving group, gives the sulfides **10.3** and **10.4**.



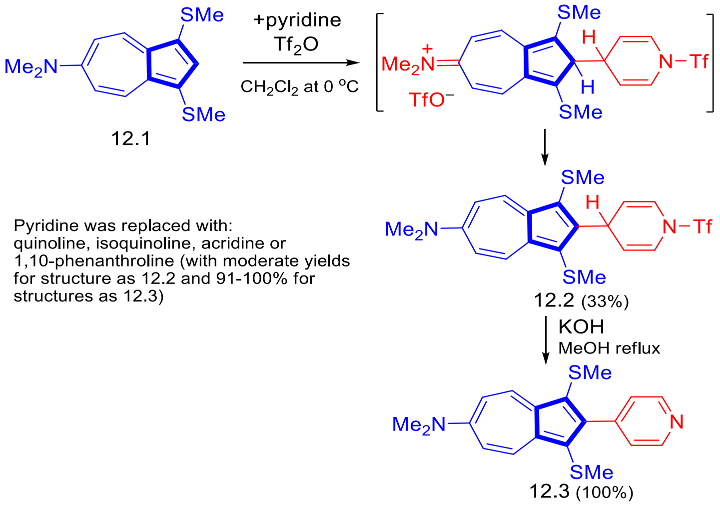
Scheme 10. Synthesis of azulenyl sulfides.

Trifluoroacetic anhydride activates the tetramethylenesulfoxide in the reaction depicted in Scheme 11 [**Error! Reference source not found.**], and the product **11.1** will be found further as starting compound in the Suzuki–Miyaura coupling reaction.



Scheme 11. Substitution of azulenes with tetramethylenesulfoxide.

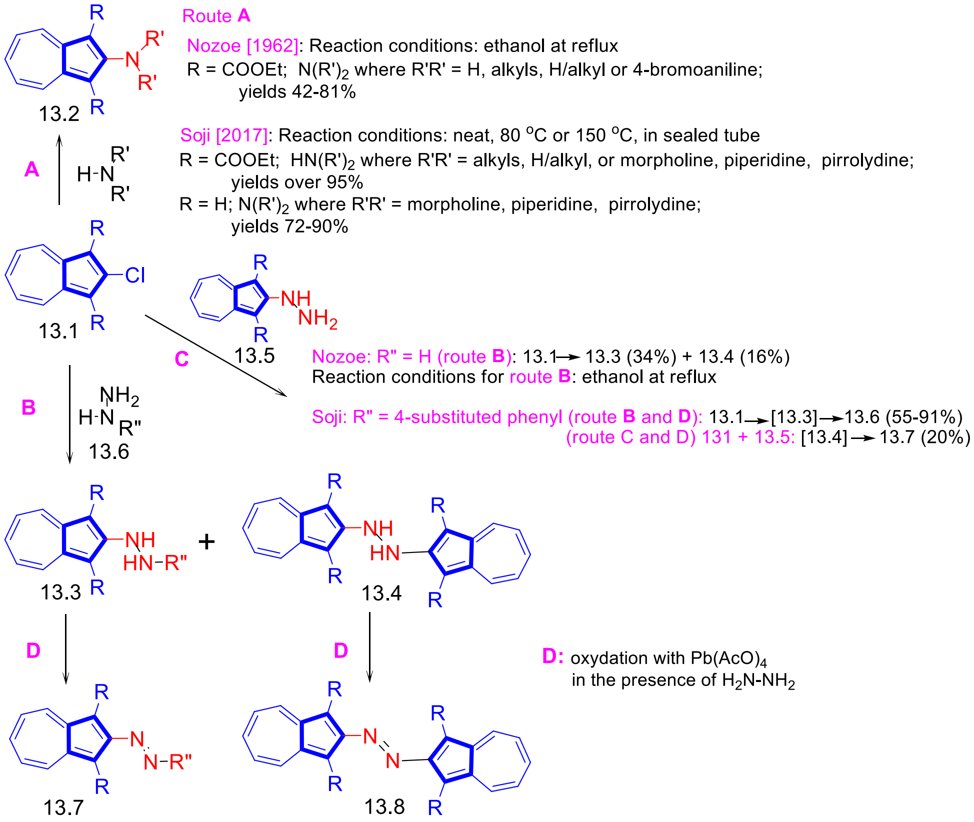
In the following, the behavior of compound **12.1**, which undergoes a SEAz reaction at position 2, is analyzed (Scheme 12) [**Error! Reference source not found.**]. The suitable structure of this compound with two protecting groups at positions 1 and 3 and with a strong electron donor, dimethylamino, at azulene position 6 allows the electrophilic attack at position 2. The substitution is performed by the efficient electrophile (TPT) depicted in Scheme 7. The intermediate compound **12.2** was aromatized to produce **12.3**.



Scheme 12. SEAz at position 2 activated by 6-NMe$_2$ group.

3.1.2. Azulene Nucleophilic Substitution, SNAz

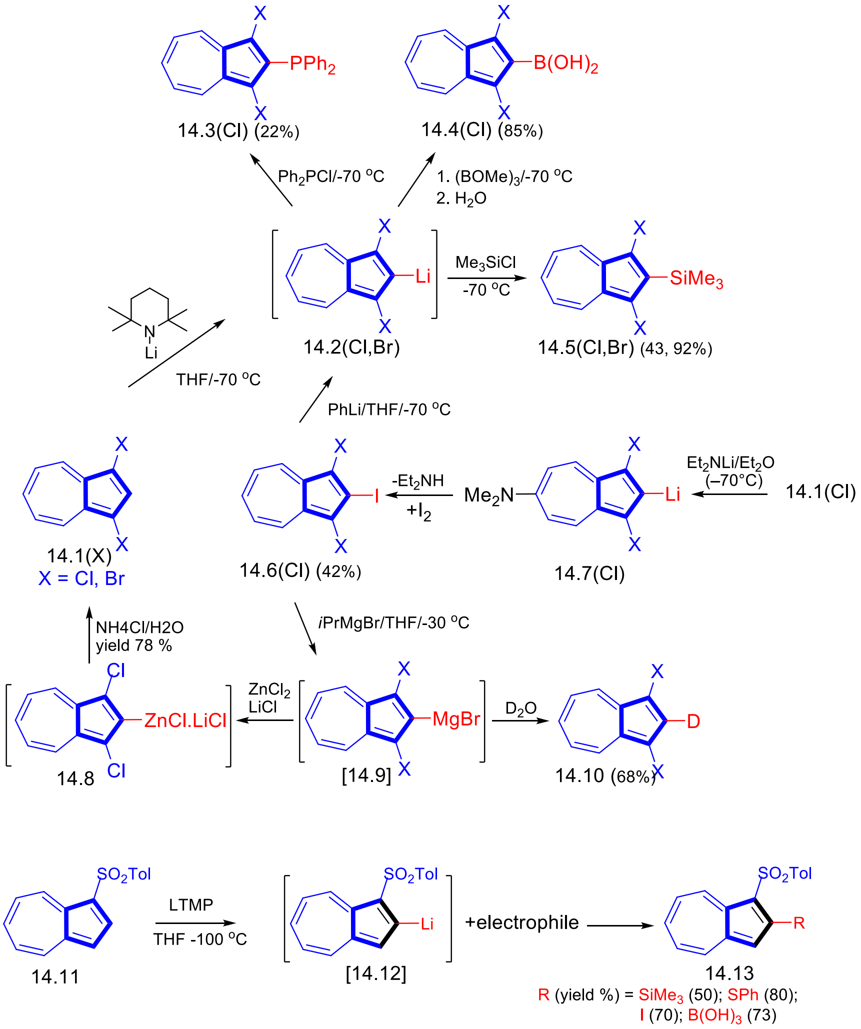
The increased electron density at the azulene five ring requires special conditions to allow nucleophilic substitutions, and if they occur, they will attack position 2, the poorest in electrons. Thus, the substitution of chlorine from position 2 requires electron acceptor groups in positions 1 and 3 of azulene, for example, CO_2Me, 13.1($R = CO_2Me$), and highly nucleophilic reagents as the amines depicted in Scheme 13, such conditions were used in 1962 by Nozoe [**Error! Reference source not found.**]. Hydrazine and hydrazo derivatives of azulenes 13.5 and 13.6 were also taken into account as starting nucleophiles. Later, Soji and coworkers repeated this substitution, but instead of ethanol used by Nozoe as reaction medium, they used neat condition at 80 °C or 150 °C in a sealed tube [**Error! Reference source not found.**]. The obtained yields were higher than those previously reported. Interestingly, the substitution occurs also in the absence of the activating groups, though only with strong nucleophilic amines and with a decrease in yield (Scheme 13). The SNAz of 13.1 with phenylhydrazine followed by the oxidation of the intermediates 13.3 or 13.4 gave 2-phenylazoazulenes 13.7 or 3.8.



Scheme 13. SNAz at position 2 in the presence of CO_2Et in positions 1 and 3 (or without substituent).

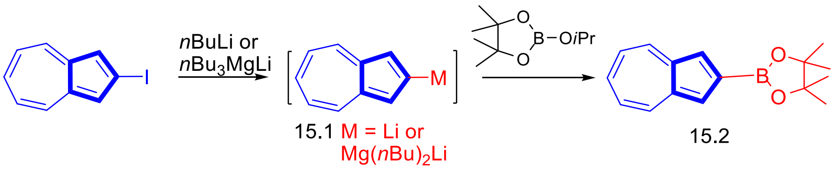
3.1.3. Metalation of Position 2 and other Substitutions at This Position

The ortho-coordination of halogen atoms situated at azulene positions 1 and 3 increases the nucleophilicity of position 2 along with an increase in acidity of hydrogen in this position [**Error! Reference source not found.**]. Thus, the proton belonging to this position can be replaced by lithium using lithium tetramethylpiperidide (LTMP) (Scheme 14), and the formed lithiated compound, 14.2, was used as starting material for several other interesting derivatives (for examples: 14.3–15.5). The lithiated compound 14.2 was also prepared following the sequence 14.1–14.7–14.6–14.2. As noted above, the increases in negative charge at the five-atom ring produced by the 6-dimethylamino group in 14.7 allowed the lithium substitution with iodine, as in 14.6. The compound 14.6 was transformed in the deuterated product 14.10 through the organomagnesium intermediate, 14.9, as shown in Scheme 14. Recently, Bredihhin and Dubovik substituted the MgBr group in 14.9 with ZnCl, giving the compound 14.8, and as shown later, used this compound in the Negishi reaction [**Error! Reference source not found.**]. As it results from Scheme 14, the SO_2Tol group has a similar influence on the azulene position 2 [39].



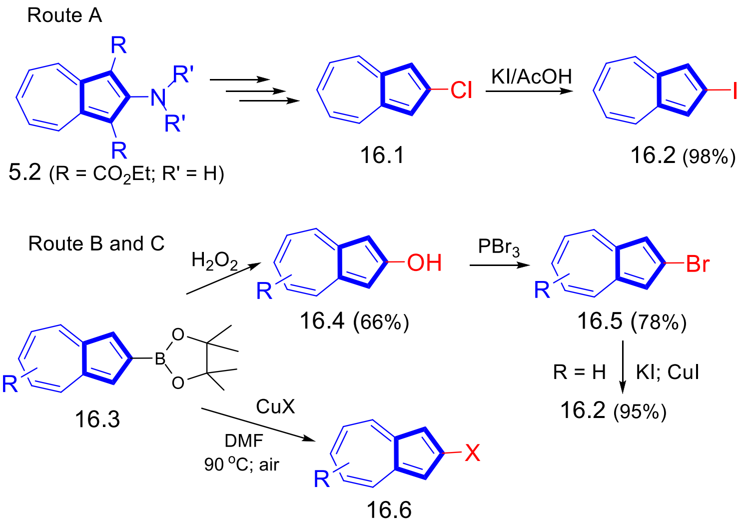
Scheme 14. SNAz at position 2 in azulene.

The 2-azulene boronate, **15.2,** one of the starting materials in the Miyaura–Suzuki reaction was obtained as shown in Scheme 15, starting from 2-iodoazulene and passing through the intermediary **15.1** [37,40]. Previously, the generation of compound **15.2** was accomplished by metal catalysis.



Scheme 15. Synthesis of 2-azulene boronate.

Despite the difficulty of substitution of the azulene 2 position, a significant number of syntheses start from 2-halogenated compounds. Scheme 13 shows, along with Nozoe's older 2-halogenoazulenes syntheses (route A) [23], the use of the boronic compounds, **16.3**, for obtaining such compounds (routes B and C in Scheme 16) [41].



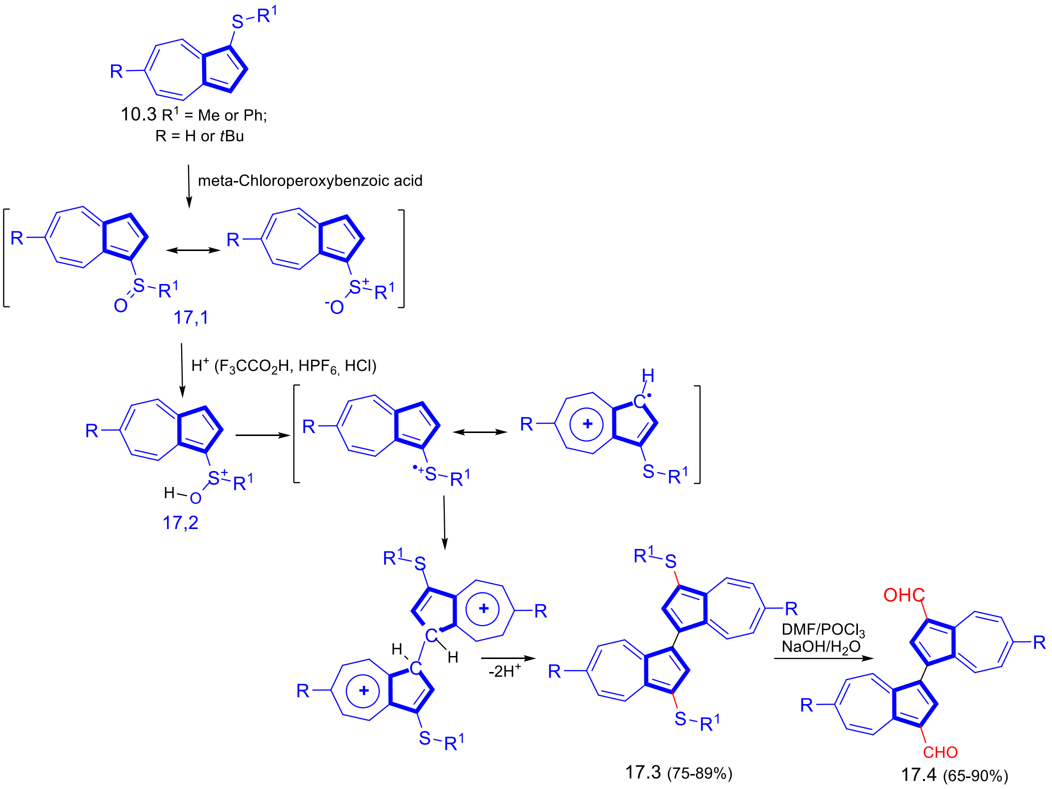
13.6 R = H; X (yield %) = I (79), Br (70); Cl (57)
13.6 R = 1,4-dimethyl-7-isopropyl; X (yield %) = I (65), Br (55); Cl (48)
13.6 X = I; R (yield %) = 4,6,8-Me_3 (62); 6-*t*Bu (75)

Scheme 16. Several routes for halogenation of azulene in position 2.

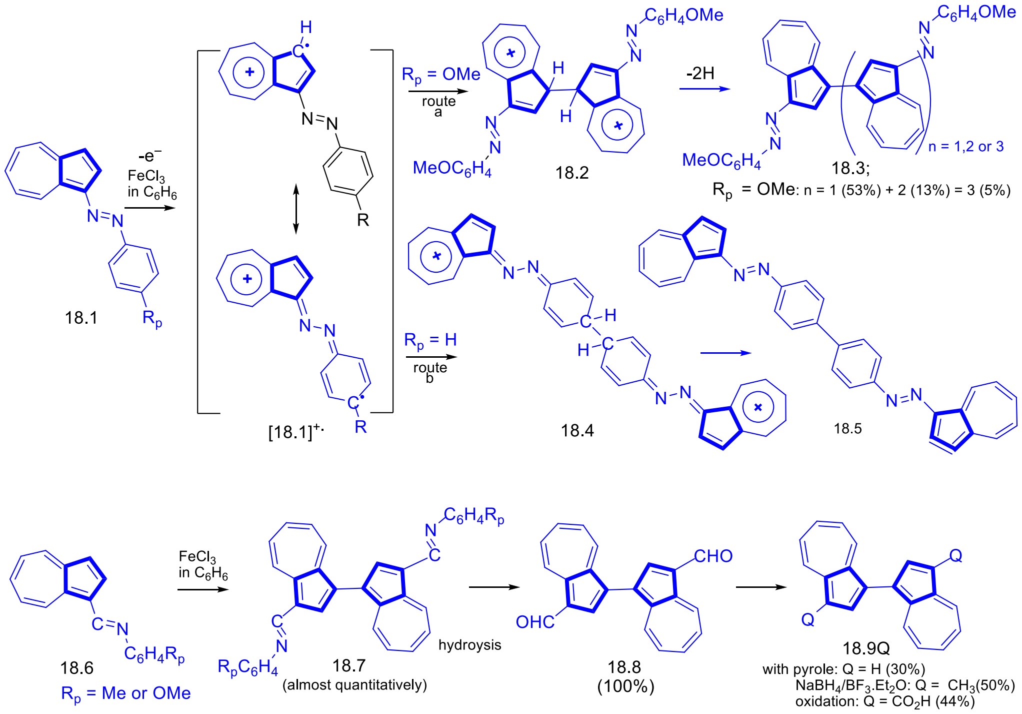
3.1.4. Radical Cation Route

Radical or radical cationic reactions are less common in the chemistry of azulenes. An example of such a reaction is the production of 1,1′-biazulenes. Over time, a series of syntheses of 1,1′-bisazulenes have been carried out [42,43]. Unlike the difficult reaction conditions reported for these syntheses, such as high temperature or transition-metal reagents, the route proposed by Soji et al., depicted in Scheme 17, is more advantageous [32,44]. The synthesis starts from the sulfide 10.3 (Scheme 10), and the formed sulfoxide 17.1 reacts with acid to give the compound 17.3 as a result of the formation of a radical cation that subsequently dimerizes. Unlike other syntheses proposed for the realization of 1,1′-bisazulenes, this route does not start from complicated azulenes, avoids the presence of metals as catalysts, and takes place with good yield. In addition, the products obtained can be used to build other molecules, such as dialdehyde 17.4.

A radical mechanism was postulated in 2000 by Razus for the oxidative dimerization of azulene azulene-1-azoarenes **18.1** [45] and N-(azulen-1-ylmethylene)arylamines **18.6** [46] in the presence of $FeCl_3$. After the loss of one electron, the dimerization of radical cation [**18.1**]$^+$ takes place in position 1 of azulene if the phenyl is substituted, route a in Scheme 18, or in position 4 of the phenyl, route b. As shown in Scheme 18, route a produces three oligomers **18.3**, whereas on route b, the compound **18.5** results. Similar behavior was noted in the case of the Schiff base **18.6.** If the yield of compounds **18.3** is more modest, the oxidation of **18.6** proceeds almost quantitatively. This is important because the product **18.7** can be transformed in the dialdehyde **18.8**, a valuable starting material for the syntheses with high yields of the interesting precursor of 1,1′-bisazulenes **18.9Q** [47].



Scheme 17. Synthesis of 1,1′-biazulenes without catalyst.



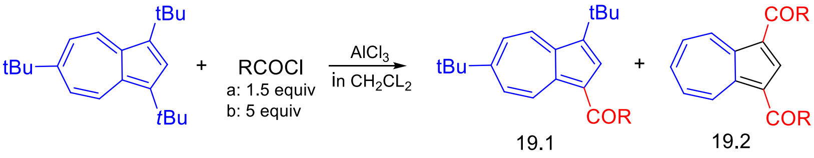
Scheme 18. Radical dimerization of azulenes at the oxidation.

3.2. Reactions Catalyzed by Metals

Interest in azulene reactions catalyzed by metal compounds is revealed by the particularly large number of articles and reviews published in this field. The interest raised in this matter is attributed to the fact that reactions take place in much milder conditions and usually with very favorable yields. However, the price of the catalysts used, as well as some ecological restrictions in relation to them, must be taken into account.

3.2.1. Aluminum Chloride as Catalyst

The use of $AlCl_3$ in reactions of azulenes can rarely be found in the literature due to the sensitivity of many azulene compounds that do not resist in the presence of this catalyst. However, at the beginning of this chapter, a recent electrophile ipso reaction catalyzed by $AlCl_3$ is presented (Scheme 19). The final acylation mixture contains amounts of mono- and disubstituted products, 19.1 and 19.2, depending on the ratio of azulene:catalyst, and the tendency toward double substitution is obvious [48].



R / yields in %
CH_3 / 19.1:19.2 for a = 31:7; for b = 0:77
C_6H_5 / 19.1:19.2 for a = 19:24; for b = 0:71

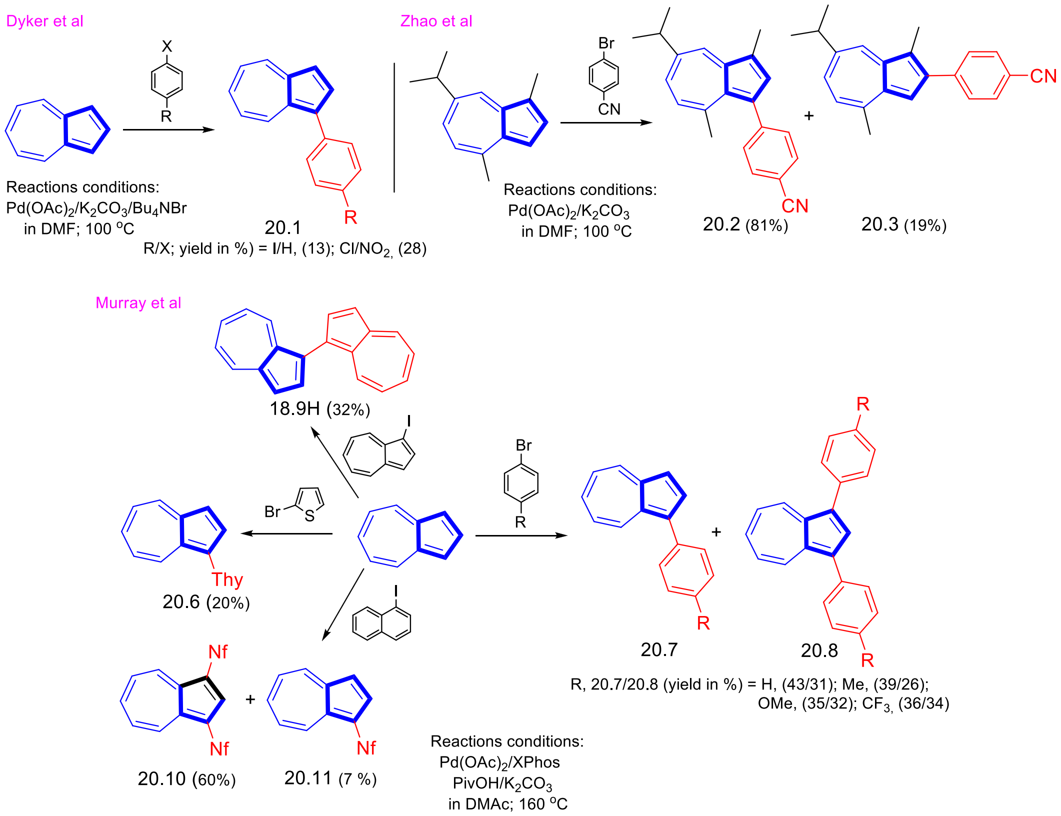
Scheme 19. Aluminum chloride as catalyst of electrophile *ipso*-substitution.

The purpose of this subchapter is to present azulenes cross-coupling reactions. Unlike the published reviews that target this very field [11,15–17,20,21], our goal will be the reactions that take place at the five azulene ring. As already written, the presentation is mostly graphic with schemes including the reaction conditions and yields, and where considered necessary, the proposed reaction mechanisms are presented.

3.2.2. Cross-Coupling Reactions

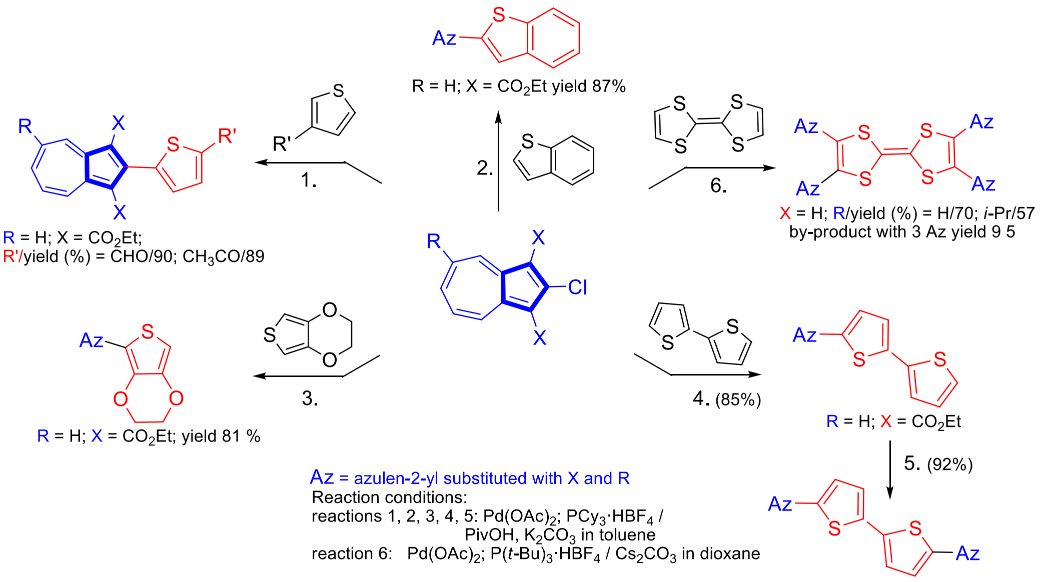
Probably the most accessed field in metal catalysis is the cross-coupling reaction that produces azulenes substituted with aromatics. A number of metal complexes, especially those belonging to the class of transition metals, have been successfully used to activate azulene positions in order to catalyze their substitution. The importance given to this research is related to both the scientific interest and the possible technical uses of the synthesized compounds.

A. Reactions catalyzed by $Pd(OAc)_2$. Dyker et al. realized the palladium-catalyzed arylation of azulene with iodobenzene or 4-chloronitrobenzene [49] and Zhao et al. arylated guaiazulene C-H bonds, as shown in Scheme 20 [50]. As in the previous procedures, the cross-coupling reactions carried out by Murai et al. used Pd(OAc)2 as Pd source (Scheme 20) [51]. As ligand for Pd, Murai added 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) to the reaction mixture, which also comprised pivalic acid (PivOH) and N,N-dimethylacetamide (DMAc). The Murai procedure takes place with the obtaining of comparable amounts of mono- and bis-product **20.7**:**20.8**, and substitution in position 2 was not observed. Murai also obtained the dimer **18.9H** in a single step, though the yield was modest (for comparison, see Scheme 18).



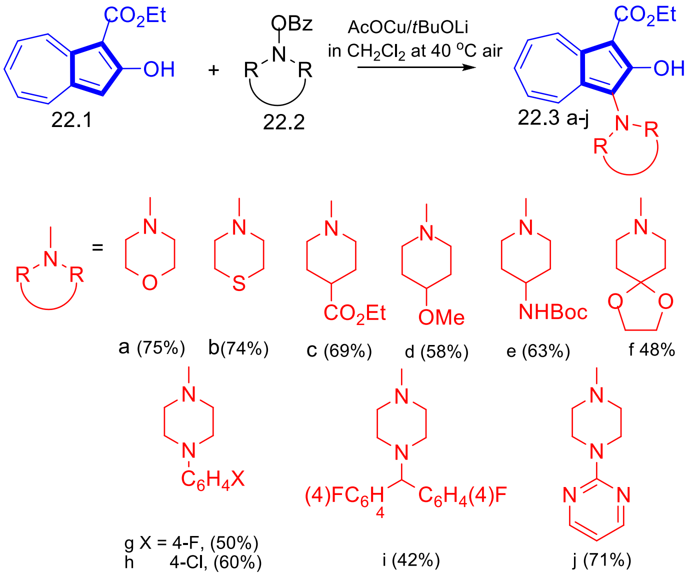
Scheme 20. Azulene arylation in the presence of Pd(OAc)2.

In more recent comprehensive studies, Soji et al. dealt with the substitution of 2-haloazulenes with thiophene derivatives [52,53]. For obtaining the products shown in Scheme 21 they used the procedure described by Schipper [54]. It should be mentioned that on routes 3 and 4, along with monosubstituted compounds, small amounts of secondary products appear as a result of bis substitution. These compounds were also obtained by the substitution of monosubstituted compounds (see route 5 in Scheme 21).

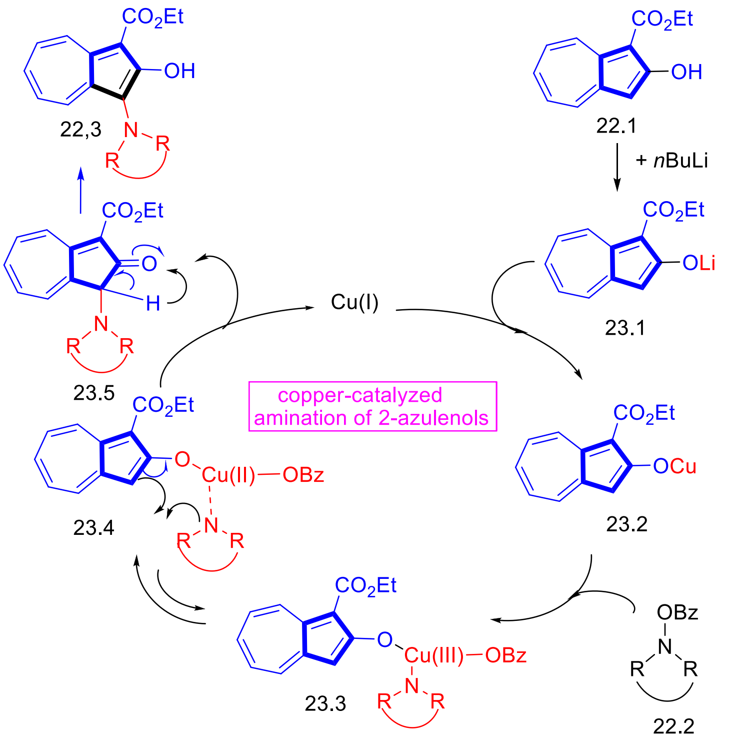


Scheme 21. Substitution of 2-halogenoazulenes with thiophene derivatives.

B. Reactions catalyzed by CuOAc. The difficulties encountered when introducing the amino group to the five-azulene ring are known, and therefore the synthesis proposed by Li and Wang [55] is interesting and will be examined further. As shown in Scheme, 22 *O*-benzoylhydroxylamines, **22.2**, were the amination reagents of 2-azulenol **22.1**. As a result of the study, a series of interesting products, described in Scheme 22, were obtained. The catalytic cycle proposed by the authors is reproduced in Scheme 23.



Scheme 22. Amination of 2-azulenols with *o*-benzoylhydroxylamines.

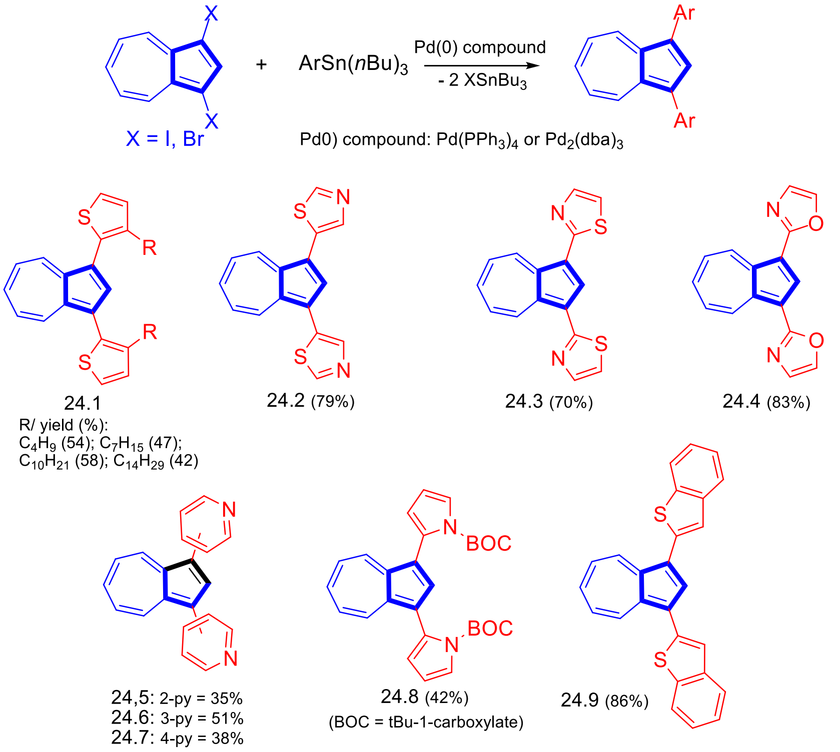


Scheme 23. Proposed mechanism for the amination of 2-azulenols with 1-benzoylhydroxylamines.

In the first step of synthesis, the lithium salt, **23.1**, was formed, then it replaced the ligand, obtaining the Cu(I) salt, **23.2**. This step is the oxidative addition of 1-benzoylhydroxylamine, which produces the Cu(I)–Cu(III) transformation, **23.3**. The equilibrium between intermediates **23.3** and **23.4** is shifted rapidly towards the last intermediate. This N-centered radical attacks azulenol at the ortho-position to give **23.5**. For this path, the authors assume "a pseudo five-membered ring through inner-sphere electron-transfer model, and at the same time to regenerate CuI to close the catalytic cycle. The rearomatization of D provides the final product **22.3**."

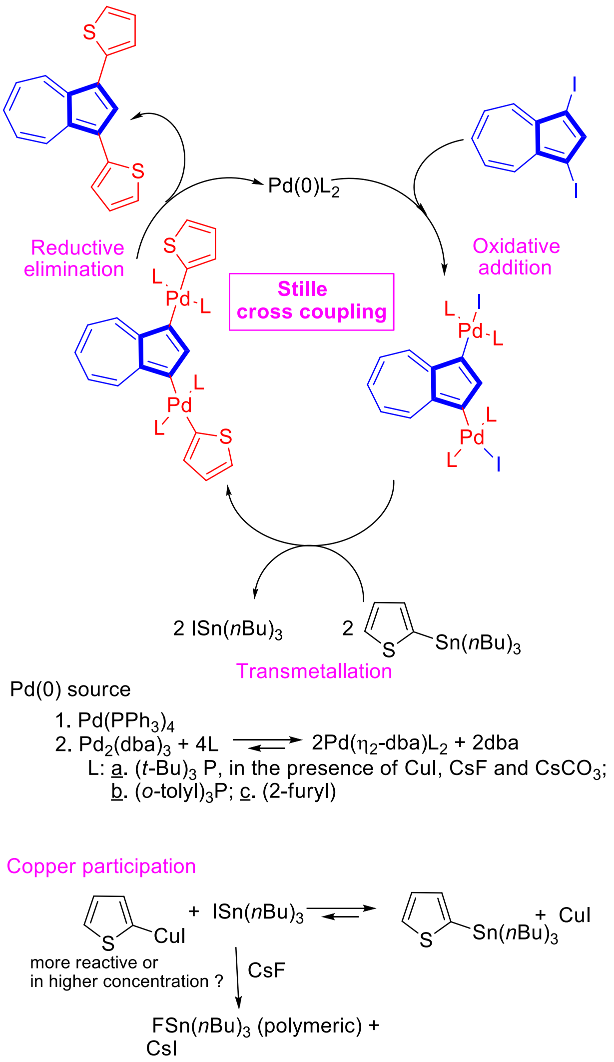
C. Stille cross-coupling reactions. Although this condensation is found in the literature mainly for obtaining bonds in the 6 azulene position, there are also examples for the substitution of positions in the five azulene ring, and some of these will be further discussed. The presence of copper as CuI brings a significant increase in the reaction yield and is therefore used in many Stille cross-couplings.

The examined Stille reaction occurs between the halogenated azulenes at five-ring and tri-*n*-butylstannyl compounds in the presence of the palladium source ($Pd(PPh_3)_4$ or $Pd_2(dba)_3$) (dba: dibenzylidenacetone) (Scheme 24). A large number of 1,3 disubstituted products generated by Stille cross-coupling are detailed in the literature. Some of these compounds are shown in Scheme 24: **1,3-**bis(thien-2-yl)azulene**, 24.1** [56], (azolyl)azulenes, **24.**(**2**-**4**) [57], 1,3-di(2-pyridyl, 3-pyridyl-3-pyridyl)azulenes, **24.**(**5**-**7**) [58,59], 1,3-di(2-pyrrolyl) azulene, **24.8** [60], **1,3-**bis(benzothien-2-yl)azulene, **24.9** [61].



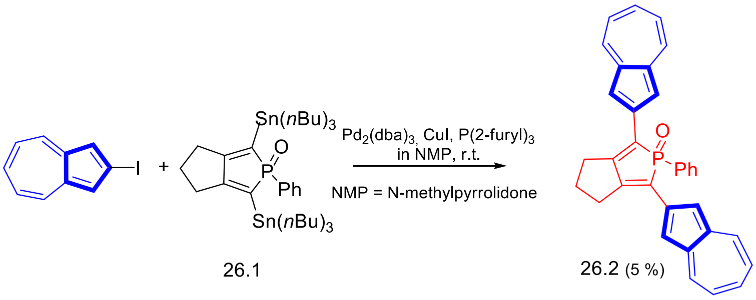
Scheme 24. Products of Stille coupling between halogenated azulene and different (tri-*n*-butyltin) substituted compounds.

The simplified mechanism of the Stille reaction based on data from the literature [62–64] is adapted in Scheme 25 to the reaction of 1,3-diiodoazulene with 2-(tri-*n*-butylstannyl)thiophene. The oxidative insertion of Pd between the halogen and the azulene ring activates the reactive positions 1 and 3 of azulene. Then, the electrophile reaction was favored by the transmetalation of organometallic nucleophiles. The reaction is promoted by the activation of organic electrophile—in our case, the azulene compound—by oxidative introduction of Pd. Then, the electrophile reaction is favored by the transmetalation of organometallic nucleophiles. The copper participation changes the stannyl group and the newly formed metallic compound seems to be more reactive or is at high concentration in the reaction medium [65].



Scheme 25. Simplified representation of the Pd-catalyzed Stille reaction and additional copper participation.

A somewhat more special example is illustrated in Scheme 26. The synthesis of 2,5-(diazulen-1-yl)phosphole *P*-oxide, **26.2**, was performed by the reaction of 2-iodoazulene and 2,5-bis(tributylstannyl)phosphole, **26.1** [66].

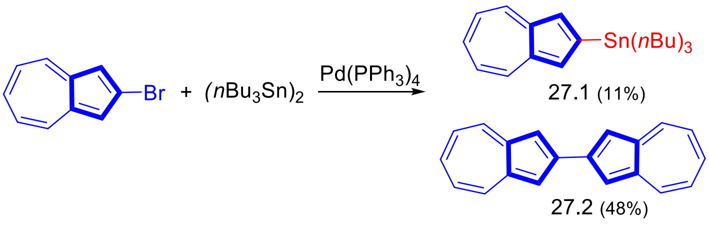


26.1

26.2 (5 %)

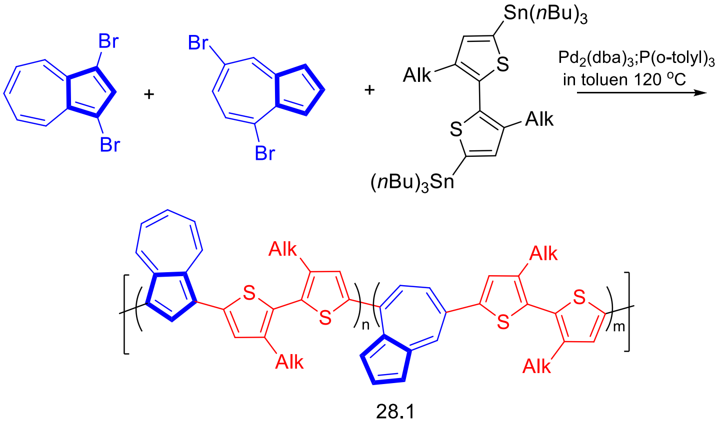
Scheme 26. Synthesis of 2,5-(diazulen-1-yl)phosphole *P*-oxide.

With the aim of activating azulene position 2, 2-bromoazulene reacted with bis(tri-*n*-butyltin) under Pd(0) catalyzed conditions. Instead of producing the attempted organometallic compound, 2-stannylazulene, **27.1**, this product results in only a 10% yield together with 2,2-biazulene, **26.2**, in 48% yield (Scheme 27) [67]. For this behavior, the authors supposed either high reactivity of metalated azulene towards 2-bromoazulene or the homocoupling of the metallized compound under the reaction conditions.



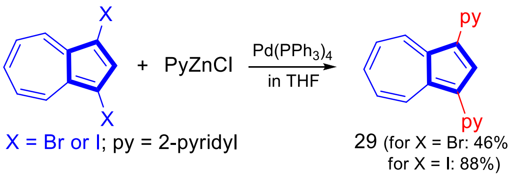
Scheme 27. Attempting to generate 2-(tri-*n*-butylstannyl)azulene.

It is noteworthy that Stille coupling has also been used to obtain conjugated co-polymers with optoelectronic properties [**Error! Reference source not found.**]. One of the attempts is represented in Scheme 28 [69], where m and n in the polymer **28.1** depend on the ratio of incorporation of dihalogenated azulene regioisomers.



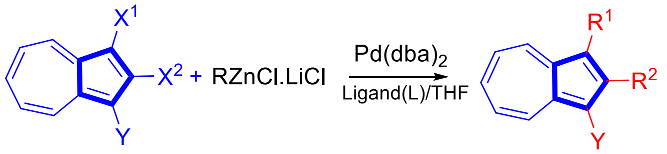
Scheme 28. Polymers containing azulene.

D. Negishi and Kumada–Tamao–Corriu cross-coupling. The family of palladium-catalyzed cross-coupling reactions includes Negishi cross-coupling as an alternative to the Stille reaction. Here, Sn was replaced by Zn in the organometallic reagent, which is coupled with halogenoazulenes in the presence of the Pd catalyst. Thus, Oda et al. reported the preparation of 1,3-di(2-pyridyl)azulene, **29**, (Scheme 29) [58] starting from 1,3-dihalogenoazulene and 2-pyridylzinc bromide in the catalytic presence of $Pd(PPh_3)_4$, with higher yield than that reported by Wakabayashi et al. for the Stille procedure used for the same coupling [59].



Scheme 29. Negishi cross-coupling.

Later, Dubovik and Bredihhin developed this cross-coupling reaction using a wide variety of organozinc compounds, even azulenylzinc derivatives, which were first synthesized by the authors (Scheme 30). At the same time, the nature of the palladium catalyst was diversified [38,59,70,71]. The organozinc compounds were obtained by treating the halogenated derivative, preferably iodide, with turbo Grignard reagent (*i*PrMgCl.LiCl), followed by transmetalation with $ZnCl_2$. The reactions were performed with ($Pd(dba)_2$) as palladium source with a ligand in THF. As ligand, SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) was preferred instead of PPh_3.



Y = Cl; X^1 = Br; X^2 = H; R^2 = H; R = R^1 = Ph L = PPh_3 or SPhos (yield 75-76%)

Y = Cl; X^1 = Br; X^2 = H; R^2 = H; R = R^1 = Z-C_6H_4- ; 4-Py; 2-Thy L =: SPhos (yield 53-87%)
(Z = H; 4-CO_2Et; 4-OMe; 3-CF_3; 3-F,4-OMe)

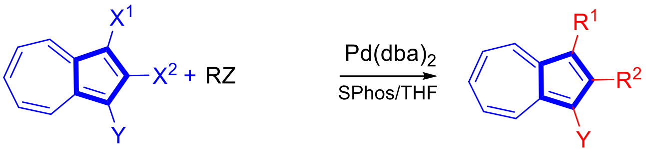
Y = CO_2Et; X^1 = Br; X^2 = H; R^2 = H; R = R^1 = *i*Pr; Z-C_6H_4-; 2-Thi; subst. fur-2-yl
(Z = 4-OMe; 3,5-$(OMe)_2$; 4-OMe); L = SPhos (yield 53 - 84%)

Y = X^2 = H; X^1 = Br; R^2 = H; R = R^1= Z-C_6H_4- L = SPhos (yield 65 - 80%)
(Z = 3-CF_3; 3-CN, 3,5-(CF_3))

Y = X^1 = H; X^2 = Br; R^1 = H; R = R^2 = Z-C_6H_4- L = SPhos (yield 76 - 86%)
(Z = 4-CO_2Et; 3-CF_3; 4Py)

Scheme 30. Negishi cross-coupling with different organozinc compounds.

As noted above [74], the azulene moiety can also act as the organometallic component Scheme 31. This coupling variant can be used if the organometallic compounds with other organic systems (as metalated pyridines and pyrimidines) are difficult to obtain.



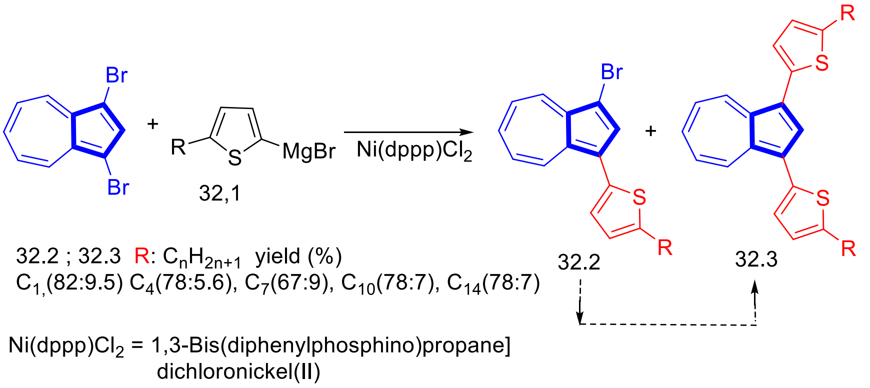
X^2 = ZnCl.LiCl; X^1 = Y = Cl;
R^1 = Cl; R = R^2 = phenyl, heteroaromatic moiety (yield 60-80%)

X^1 = ZnCl.LiCl; Y = Cl; X^2 = H;
R^2 = H; R = R^1= unsubstituted or substituted phenyl (yield 30-39%)

X^1 = Y = H; X^2 = ZnCl.LiCl;
R^1 = H; R^2 = 2-Thy (yield 36%)

Scheme 31. Negishi cross-coupling with azulenylzinc compounds.

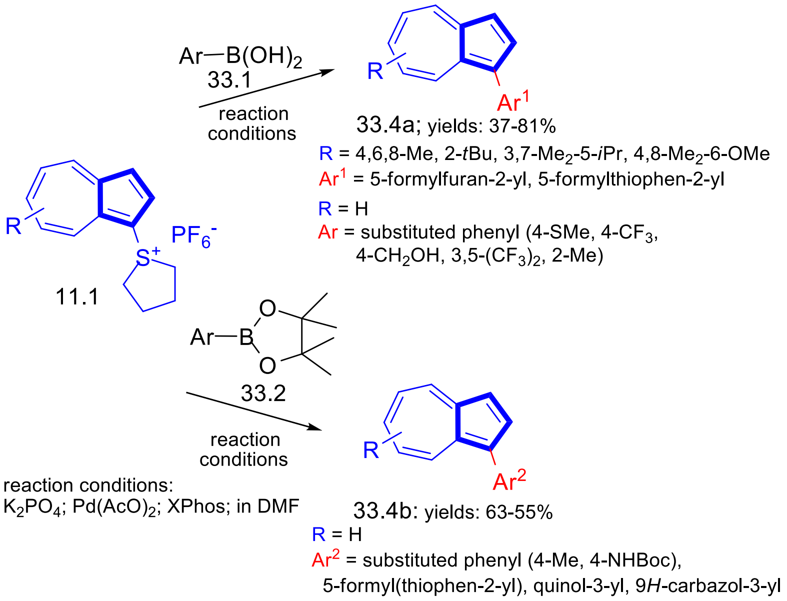
The Kumada–Tamao–Corriu synthesis that is exemplified next is similar to the Stille reaction, the metal substituent Sn(*n*Bu)$_3$ being replaced by MgCl. Thr reaction was performed with (5-alkylthiophen-2-yl)magnesium bromides, **32.1**, and 1,3-dibromoazulene and was catalyzed by $Ni(dppp)Cl_2$ (Scheme 32). The main catalytic cycle is similar to that proposed for the Stille reaction [71]. The product mixture contains—besides the disubstituted product, **32.2**—the monosubstituted one, **32.3** [73,74]. Further, the monosubstituted azulene may react with another organomagnesium reagent, affording compound **32.3**, used for preparation of stimuli-responsive conjugated copolymers with azulene and bithiophene units in the polymer backbone.



Scheme 32. The Kumada–Tamao–Corriu reaction.

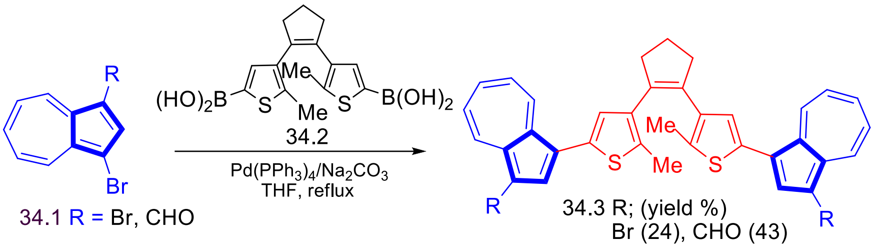
E. Suzuki–Miaura coupling. Perhaps one of the most common cross-coupling reactions is the Miyaura–Suzuki reaction [75], so it is not surprising that a great number of reviews from the azulene field paid attention to this topic. For this reason, only a few references will be pointed out, mainly for information, especially the more recent ones. As the starting materials in these reactions, boronic compounds may contain the boronic substituent either to azulene or to the compound chosen to react with it. The boronic derivatives replace other substituents, mainly halogen, in the presence of a catalyst and ligand.

Both borylation reagents, boronic acids, **33.1**, and pinacolboranes, **33.2** (Scheme 33), were used with the specification that compound **33.2** sometimes produces secondary reactions [33]. The known instability of 1-halogenoazulene suggested the idea of coupling boronic compounds with 1-azulenesulfonium salt **11.1** with acceptable yields, as shown in Scheme 33.



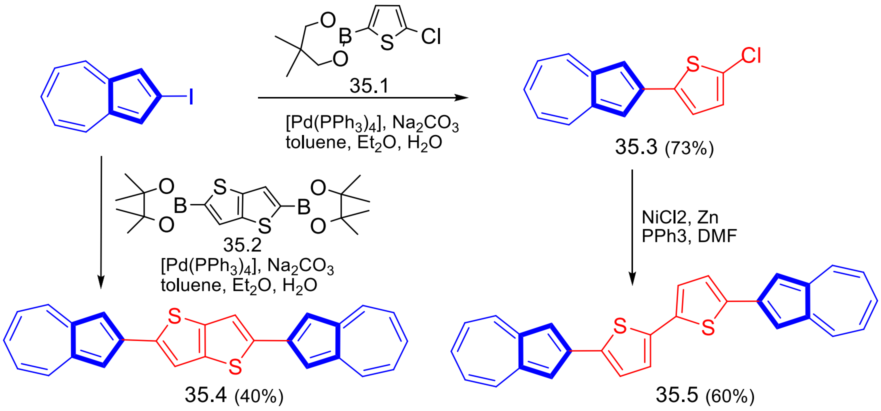
Scheme 33. Different behavior of borylation reagents.

The stability of 3-bromoazulenes **34.1** allowed the generation of photoswitch compounds **34.3** (Scheme 34) [76]. Compound **34.2** is involved in the synthesis. This reagent was used without separation after the treatment of the corresponding dihalogenated derivative with B(OBu)3.



Scheme 34. Obtaining the photoswitch compounds **34.3**.

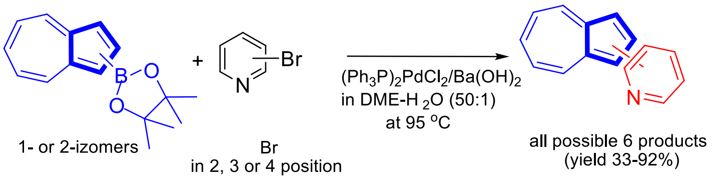
The stability of halogenated azulenes in position 2 favors them for cross-coupling reactions with boronic compounds. In Scheme 35, the starting 2-iodoazulene reacts with 5-chlorothiophene-2-boronic acid pinacol ester or thienothiophene diboronic acid ester **35.1** or **35.2**, affording 2-(2-azulenyl)-5-chlorothiophene **35.3** and 2,5-di(2-azulenyl)-thieno [3,2-b]thiophene, **35.4** [77]. The dimerization of compound **35.3** gives **35.5**. Both **35.4** and **35.5** are tested as OFETs (organic field-effect transistors).



Scheme 35. Reaction of 2-iodoazulene with pinacol esters **35.1** or **35.2**.

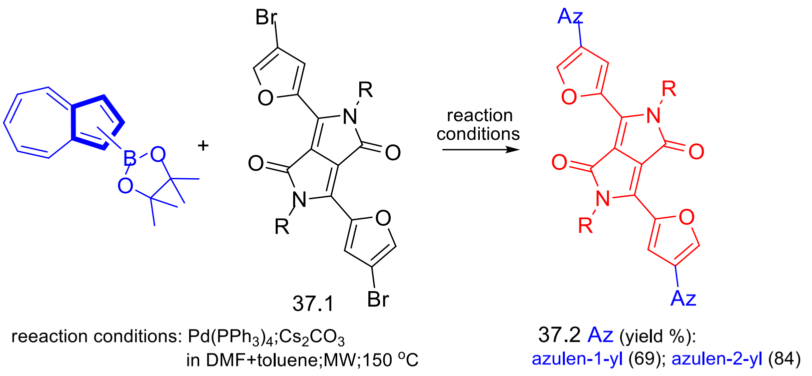
After several reactions presented above in which azulene derivatives react with boronic derivatives, reactions in which the boronic group is linked to the five azulene ring follow. Again, it must be remembered that a large part of the research undertaken in this field refers to substituted products at the seven ring of azulene.

In Scheme 13, two reactions of 2-azulenylboronate were anticipated, and in Schemes 36 and 37 are exemplified the reactions starting from both isomers of azulenylboronate. Scheme 36 briefly represents the coupling performed by Wakabayashi et al. [59] between these isomers and 2-, 3-, and 4- bromopyridines with moderate to very good yields.



Scheme 36. Coupling between azulenylboronates and bromopyridines.

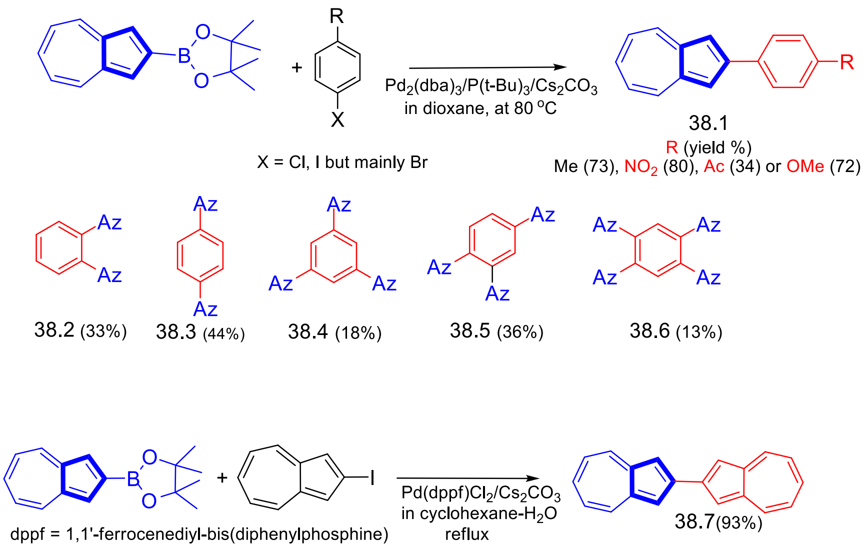
Another heterocyclic compound, furan, found in the structure of 3,6-bis(5-bromo-2-furyl)pyrrolo[3,4-c]pyrrole-1,4-dione, **37.1**, was coupled with the two isomers of azulenylboronate, and the resulting products, **37.2**, have chromophore properties [78].



Scheme 37. Coupling between azulenylboronates with compound with furan moieties.

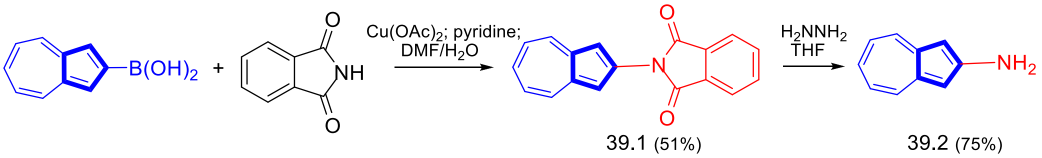
Although using only azulen-2-ylboronate, Ito et al. obtained a large number of compounds in the cross-coupling with polybrominated aromatic compounds 1,2-di-, 1,4-di-, 1,3,5-tri-, 1,2,4-tri-, and 1,2,4,5-tetrabromobenzene (Scheme 37) [40].

In an article that refers to the synthesis of 2-halogenozulene, the authors also describe the synthesis of 2,2′-bisazulene, **43**, with the highest yield starting from azulen-2-ylboronate and 2-iodoazulene, as shown in Scheme 38 [41]. Schemes 17 and 18 show the obtaining of isomer 1,1′, **18.9** [32,44,47] and the isomer 2,2′ appears in Scheme 27 [67].



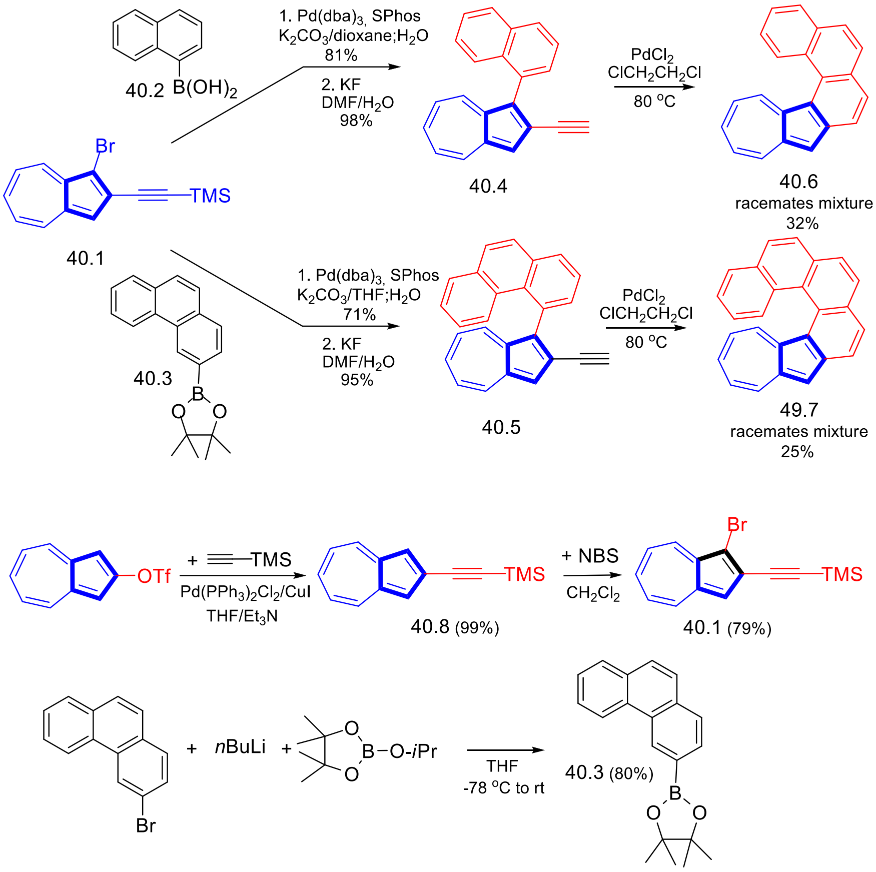
Scheme 38. Coupling between azulen-2-yl boronate and halogenated compounds.

Among the procedures proposed by Kurotobi et al. for azulene substitution in position 2, that of 2-aminoazulene (Scheme 39), a building block for the synthesis of other molecules, is also present [79]. The synthesis starts from azulen-2-ylboronic acid, which is coupled with phtalimide and the intermediate product, **39.1**, is transformed in the amine **39.2**.



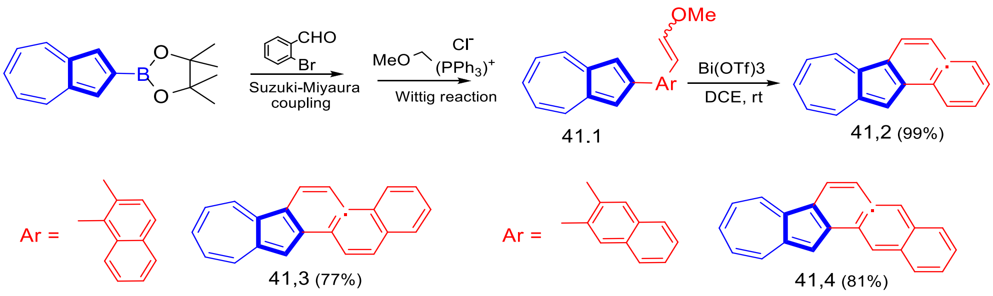
Scheme 39. Synthesis of 2-aminoazulene.

Recently, Gao et al. realized the synthesis of the wonder azulene-embedded [n]helicenes **40.6** and **40.7**, in which one terminal azulene subunit was fused with n-2 benzene rings, compounds with valuable physicochemical and optical properties [80]. Scheme 40 depicts the sequential Suzuki–Miyaura condensation of starting **40.1** to intermediates **40.4** or **40.5** followed by cycloisomerization, which leads to the products. The same Scheme shows the preparation of two starting reagents, **40.1** and **40.3**.



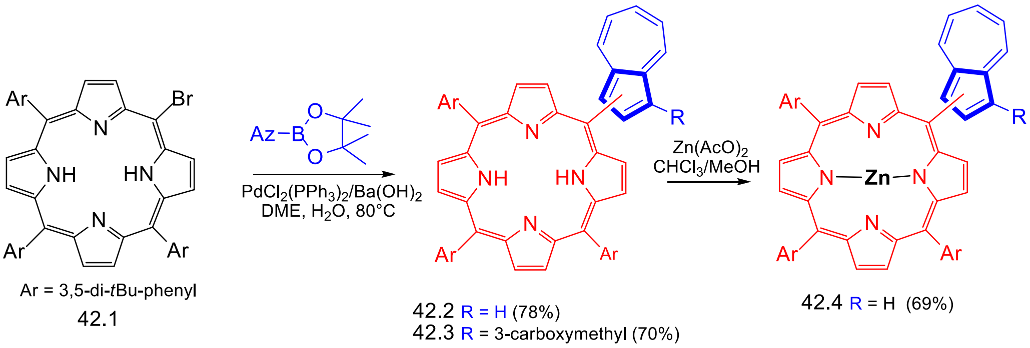
Scheme 40. Synthesis of azulene-embedded [n]helicenes.

Murai et al. described compounds with the structure shown in Scheme 41 somewhat related to the [n]helicenes presented above. After Suzuki–Miyaura coupling of azulen-2-ylboronate with aromatic aldehydes followed by Wittig condensation, the obtained intermediate **41.1** was cyclized and aromatized, affording **41.2** [81]. Similar azulene-fused linear polycyclic aromatic hydrocarbons azuleno[2,1-a]-phenanthrene, **41.3**, and azuleno[2,1-a]-anthracene, **41.4**, were generated in the same way. The azulene derivatives **4.1–4.3** have narrow bandgaps, excellent photooxidative resistance, and good solubility.



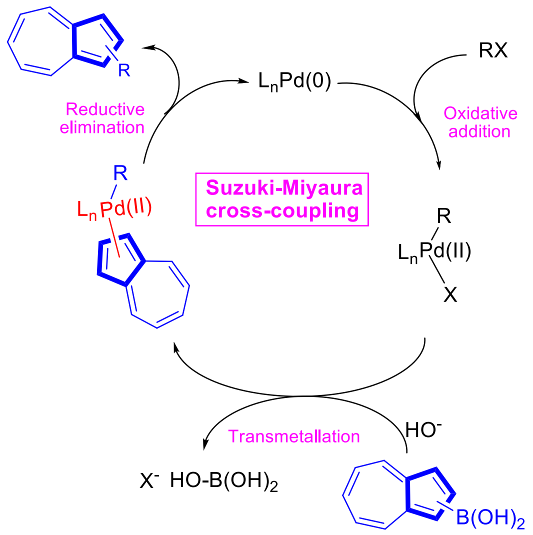
Scheme 41. Azulene-fused linear polycyclic aromatic hydrocarbons.

The spectacular *meso*-azulenylporphyrins **42.2** and **42.3** obtained by involvement of Suzuki–Miyaura coupling as shown in Scheme 42 [82], act as electron-donating and electron-accepting substituents toward Zn(II) porphyrin **42.4**.



Scheme 42. Synthesis of *meso*-azulenylporphyrins.

At the end of this subchapter, a short discussion on the steps of Suzuki–Miyaura cross-coupling is useful. Scheme 43 adapts to boronic compounds the general mechanism proposed by Miyaura [75]. A similarity should be noted between this mechanism and that described in Scheme 25 for Stille reaction. The difference consists in transmetalation, which here changes the boronic substituent of boronic reagent, instead of Sn(*n*Bu)₃.

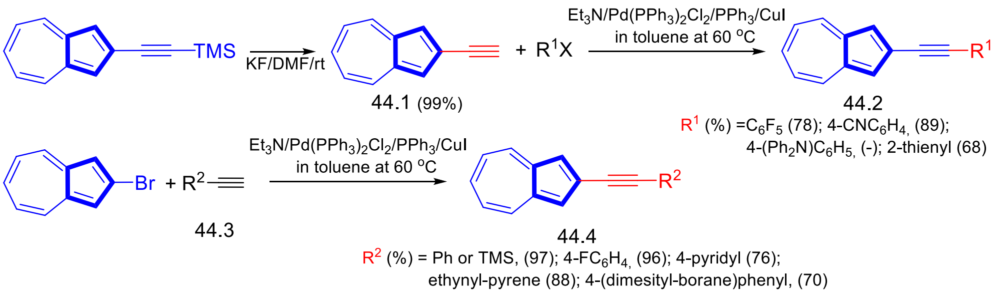


Scheme 43. Simplified representation of Suzuki–Miyura reaction pathway.

3.3. Various Azulene Five-Ring Substitutions

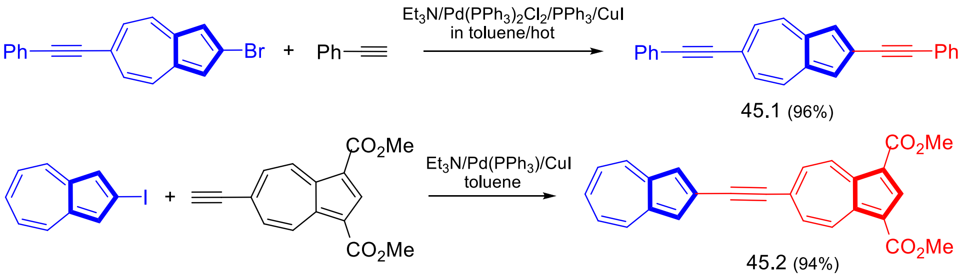
3.3.1. Azulene Alkynylation and Sonogashira–Hagihara Reaction of the 1,3-diethynylazulene

The Sonogashira–Hagihara reaction occurs between ethynyl derivatives and halogenated compounds (X = I or Br). The ethynyl group can be substituted at the five azulenic ring, compound 44.1, or can be inserted into various suitable reagents, 44.3, as shown in Scheme 44. The yields of products 44.2 and 44.4 are very good [83].



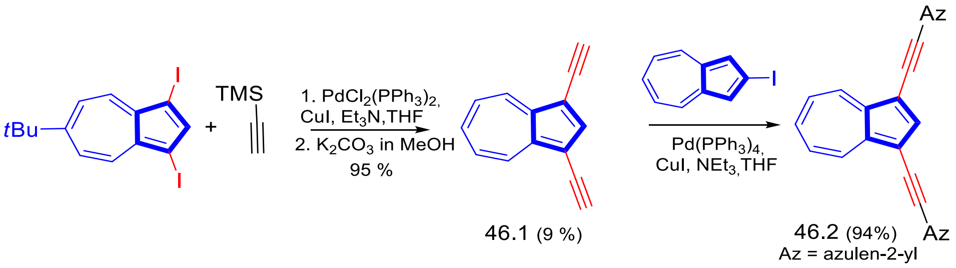
Scheme 44. Sonogashira–Hagihara reaction.

The Sonogashira–Hagihara reaction afforded also the valuable compounds **45.1** [84] and **45.2** (Scheme 45) [85]. These linear π-conjugated molecules have optical properties and stimulus-responsive behavior.



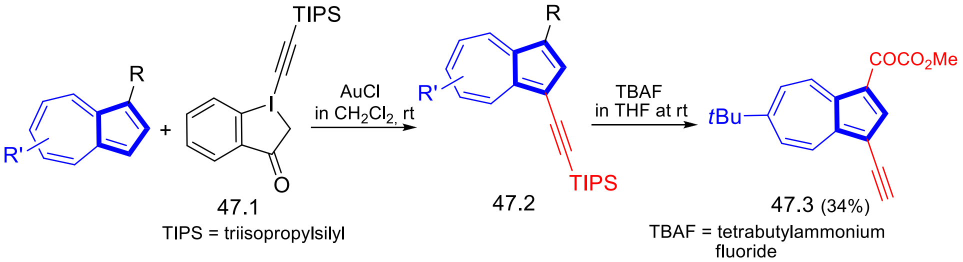
Scheme 45. Obtaining of linear π-conjugated molecules.

In a large study undertaken by Shoji on the reaction of tetracyanoethylene with 1,3-bis(azulenylethynyl)azulenes, the intermediate **46.1** and the reagent **46.2**, together with other similar compounds, were prepared with higher yields, as per Scheme 46 [86].



Scheme 46. Preparation of 1,3-bis(azulenylethynyl)azulenes.

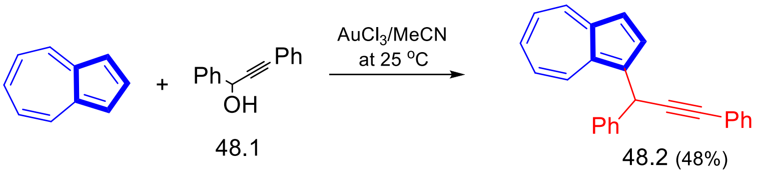
The ethynylation procedure proposed by Székely is particularly advantageous, starting directly from an unsubstituted azulene position (Scheme 47) and proceeding under mild conditions [87]. The proposed procedure is general, using triisopropylsilylethynyl-1,2-benziodoxol-3(1H)-one (TIPS-EBX, 2), **47.1** as an efficient alkynylating agent. The use of Au as an activating metal instead of Pd should be emphasized.



47.2 R with R' (yield in %) = H; 3,7-Me_2-5-*i*Pr (73); 6-Me-3-I (35);
CHO; with R' = H (44); Me (69); 4,6,8,-Me_3 (32); *t*Bu (57); Ph (79); CH_2CO_2Et;
$COCH_3Cl$; with R' = H (71); Me (57); *t*Bu (67); Ph (69);
$COCO_2Me$; with R' = H (39); Me (59);4,6,8,-Me_3 (53); *t*Bu (67); Ph (53); CH_2CO_2Et (42)

Scheme 47. Ethynylation procedure using TIPS-EBX, 2, **47.1**, as reagent.

The alkylation reagent in Scheme 48, **48.1**, also introduces the triple bond, as in molecule **48.2**. As in the previous reaction, an Au compound activates the substitution [88].

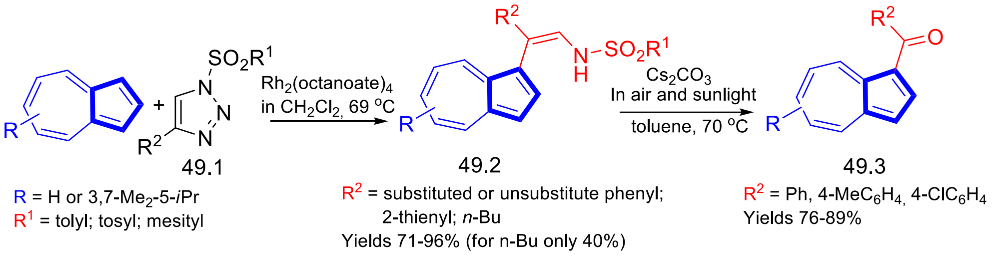


Scheme 48. Alkylation with propargylic alcohol **48.1**.

3.3.2. Various Reactions in the Presence of Rhodium or Nickel Compounds

The metal found in most of the catalysts and discussed so far was palladium, and only in a few examples are copper or gold present. Since these are not the only metals used for this purpose, in the following, the presence of other metals is also briefly exemplified. Thus, the alkylation with propargylic alcohols (see Scheme 48) occurs similarly when a thiolate-bridged diruthenium complex works as a catalyst, instead of the compound containing Au [89].

Taking into account the difficulties reported in the literature for the acylation of azulenes, Lee et al. achieved a synthesis that can produce azulene ketones with good yields [90]. In the first step, rhodium-catalyzed reaction between azulene and N-sulfonyl-1,2,3-triazoles, **49.1**, affords the N-sulfonylaminoalkenylated intermediate, **49.2** (Scheme 49). The attempted ketones **49.3** result after the oxidative cleavage of the C=C bond of N-sulfonyl enamides **49.2** in the presence of Cs_2CO_3 in air and sunlight. A plausible mechanism for the last somewhat strange reaction step based on the involvement of air oxygen was proposed by the authors.



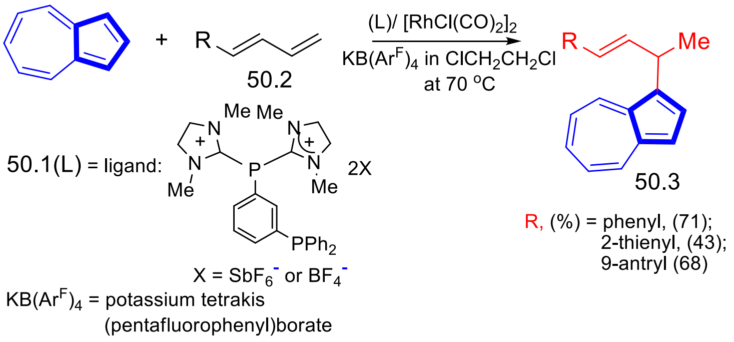
R = H or 3,7-Me$_2$-5-*i*Pr
R^1 = tolyl; tosyl; mesityl

R^2 = substituted or unsubstitute phenyl; 2-thienyl; *n*-Bu
Yields 71-96% (for n-Bu only 40%)

R^2 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$
Yields 76-89%

Scheme 49. Acylation of azulenes.

The conditions exemplified in Scheme 50 for the hydroarylation of azulene involve, besides the Rh catalyst, α-dicationic chelating phosphines, **50.1**. The allyl-substituted azulenes **50.3** result in moderate yields after the reaction between azulene and diene **50.2** [91].

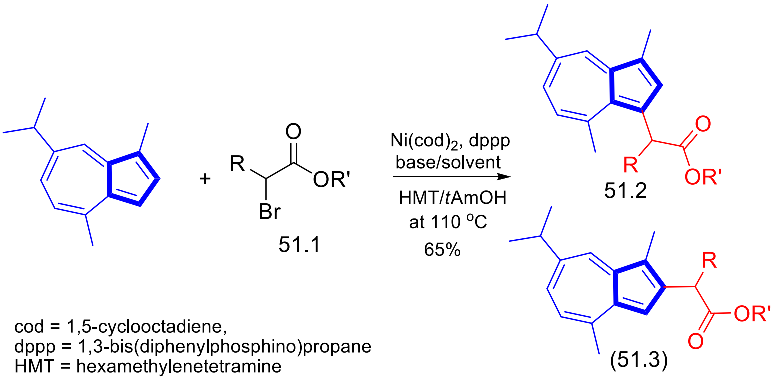


X = SbF$_6^-$ or BF$_4^-$
KB(Ar^F)$_4$ = potassium tetrakis (pentafluorophenyl)borate

R, (%) = phenyl, (71); 2-thienyl, (43); 9-antryl (68)

Scheme 50. Preparation of allyl-substituted azulenes catalyzed by a rhodium catalyst.

Nakatani et al. realized the alkylation of guaiazulene with the halogenated compound **51.1**, as shown in Scheme 51, using a nickel compound, Ni(cod)$_2$, with dppp as ligand in the presence of a base. The reaction occurred with acceptable yield; however, unfortunately, both 1- and 2-alkylated isomers, **51.2** and **51.3**, resulted [92].

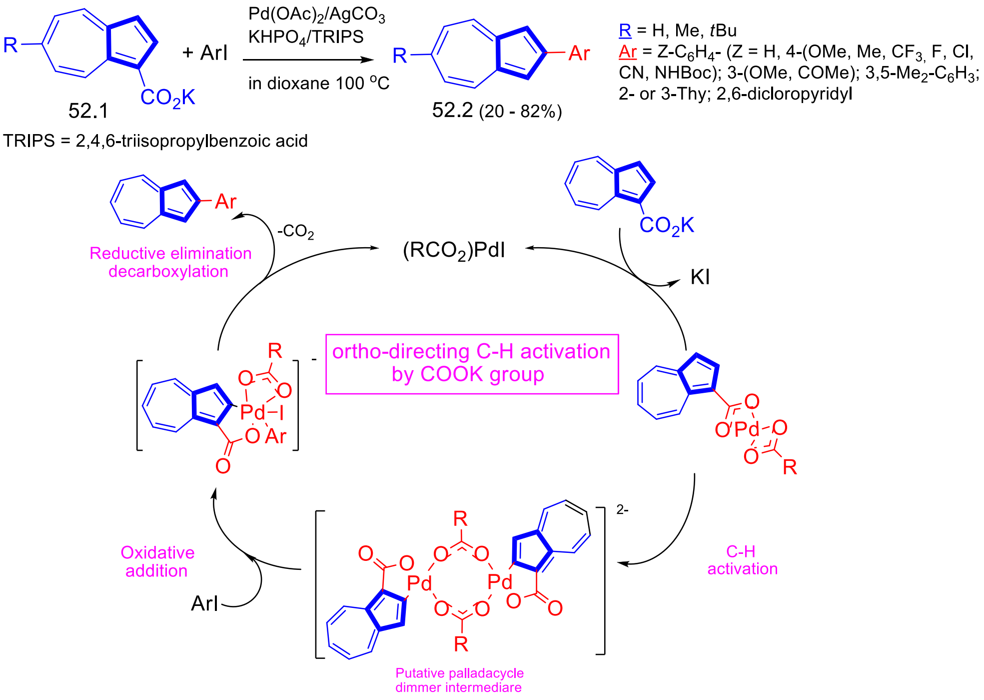


cod = 1,5-cyclooctadiene,
dppp = 1,3-bis(diphenylphosphino)propane
HMT = hexamethylenetetramine

Scheme 51. Guaiazulene alkylation using Ni(cod)$_2$ as catalyst.

3.3.3. Some More Special Reactions at the 5th Ring

Recently, Png et al. applied the peculiar ortho-arylation of benzoic acid procedure [93] to the similar azulenic acid 52.1 [94]. In this way a large variety of 2-arylazulenes 52.2 are synthesized (Scheme 52). To explain the course of the reaction, the authors assume that "the reaction likely proceeds through a carboxylate group directed C–H activation to form a putative palladacycle dimer intermediate which then undergoes oxidative addition by the aryl iodide to form a Pd(IV) intermediate (Scheme 52). Subsequent reductive elimination followed by decarboxylation yields the 2-aryl azulene products."



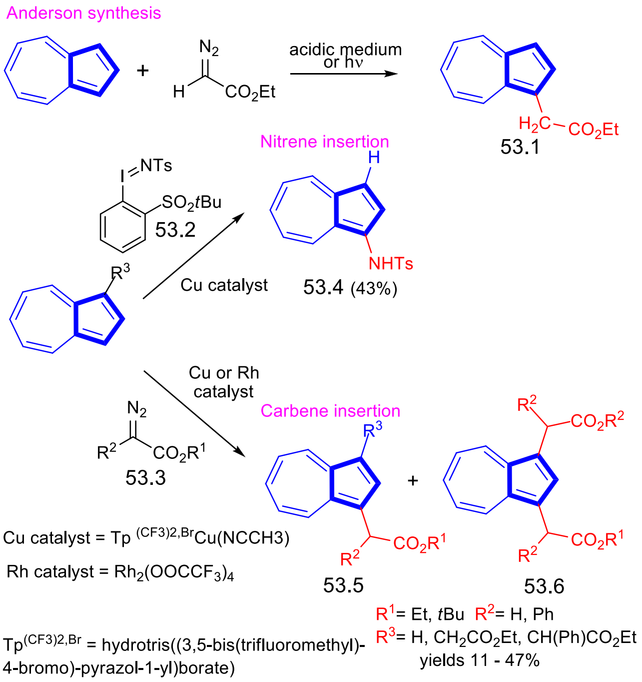
Scheme 52. Catalytic cycle proposed for carboxylic acid directed C−H arylation.

Anderson et al. realized the reaction of azulene with aliphatic diazo derivatives already in 1965. The acidic medium or the light presence ensured a moderate yield for several products, one of which, **53.1**, is shown in Scheme 53 [95]. The compounds substituted at 1 or 1 and 2 positions of azulene were realized by Carreras et al. by incorporation of carbene/nitrene in C-H bond [96]. The nitrene transfer from N-tosyliminoiodanes derivatives **53.2** to azulene or its functionalization with diazoacetates **53.3** in the presence of Rh or Cu catalysts (Scheme 53) generates the compounds **53.4** and **53.5**, respectively. Under certain conditions, the disubstituted compound **53.6** is also formed.

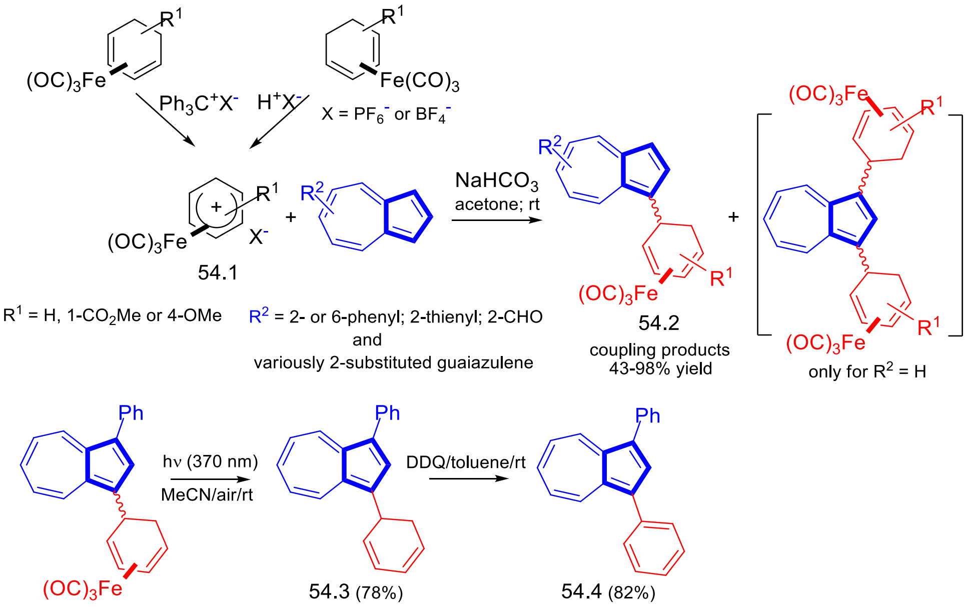
Recently, Murfin et al. functionalized azulenes with cationic η^5-iron carbonyl diene complexes [97]. To the three used electrophilic iron complexes, **54.1**, azulenes were added, as depicted in Scheme 54, affording the products **54,2** with 43–98% yield. In the Scheme, the pathway is exemplified for generation of the products with phenyl as substituent after photolytic decomplexation of addition products and aromatization of free diene: **54.2–54.3–54.4**.

3.3.4. Heterocycle-Substituted and Fused Azulenes That Involve the Five-Membered Ring

Although Soji and Ito et al. have published comprehensive reviews on heterocycle-substituted and fused azulenes [15–17], to complete the topic proposed in the current review, some examples for the obtaining of these products will be given based on the most recent information. Syntheses in which the heteroaromatic system is substituted as such at azulenes were previously discussed. Apart from this pathway, the azulenes can be substituted with precursors of the heteroaromatic rings, and in a subsequent step they are transformed into the desired heteroaromatics. Another target of this subchapter is focused on the reactions affording derivatives where azulene is condensed with aromatic or heteroaromatic rings. Among the investigated reactions for the building of heterocycles substituted at the five-atom azulene ring, only recent examples are given below, namely, the generation of derivative containing the furan and pyrrole moiety. In addition to obtaining these compounds, the recent syntheses of several systems in which azulene is substituted with other heterocycles is also analyzed.

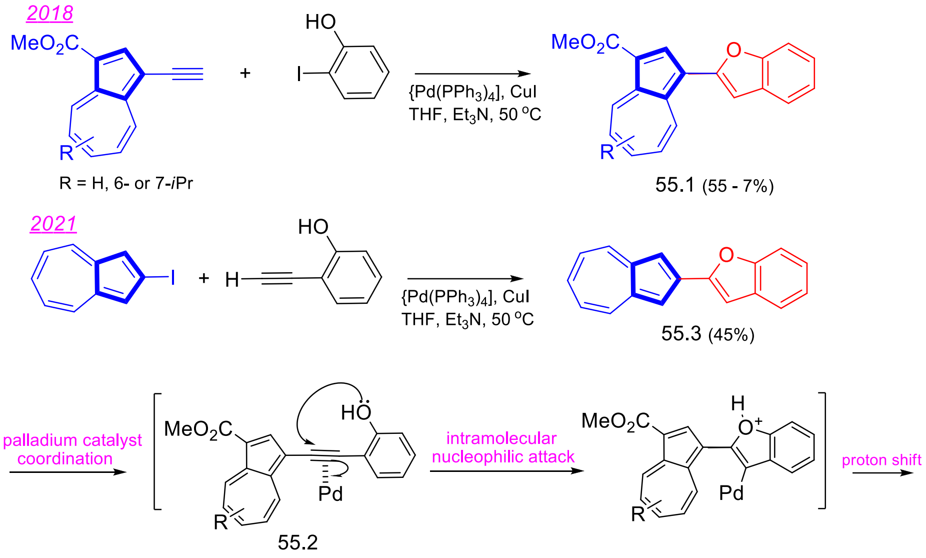


Scheme 53. C−H bond functionalization by carbene–nitrene transfer.



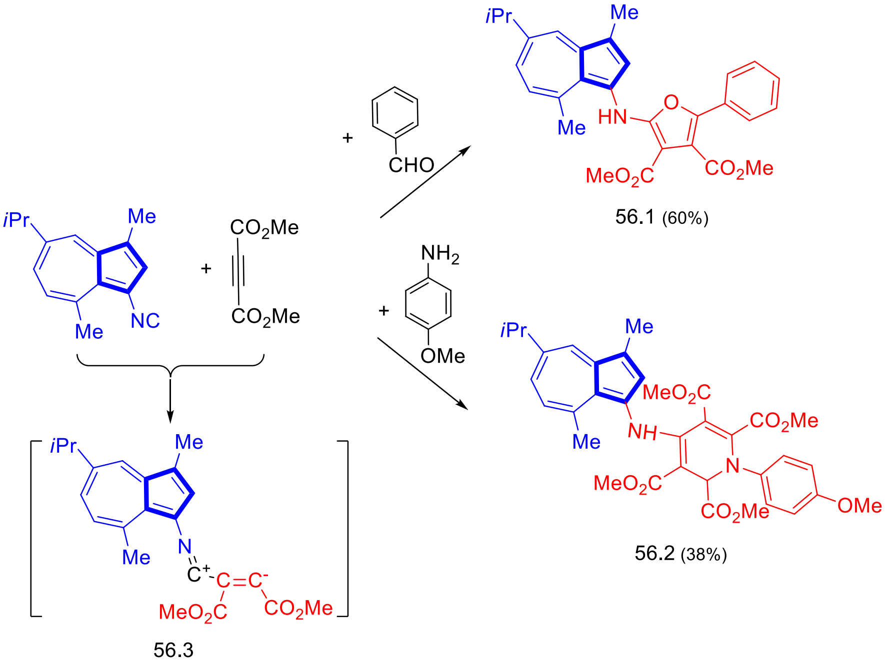
Scheme 54. Functionalized azulenes with cationic η^5-iron carbonyl diene complexes.

The 2-(Azulen-1-yl)benzo[b]furans, **55.1**, were obtained via cross-coupling Sonogashira–Hagihara reaction of 1-ethynylazulenes with 2-iodophenol, followed by intramolecular cyclization of the produced intermediate, **55.2**, as shown in Scheme 55 [98]. For the similar 2-(azulen-2-yl)benzo[b]furan, **55.3**, the reaction starts from 2-ethynylphenol and 2-iodoazulene [99]. Scheme 55 shows the mechanism proposed by the authors for the discussed syntheses.



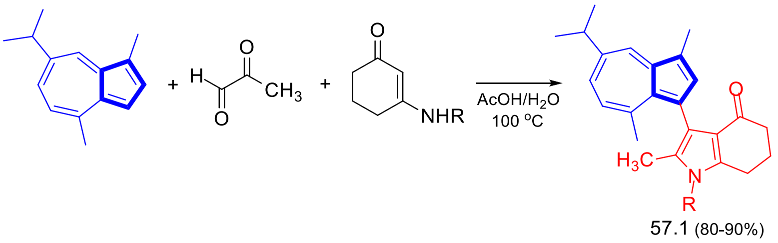
Scheme 55. 2-(Azulenyl)benzo[b]furans syntheses.

In the following, some multicomponent reactions are presented that allow the obtaining of azulenes functionalized with heterocycles. The reactions reported by Sato et al. afforded guaiazulene–heterocycle hybrids, **56.1** and **56.2**, via a zwitterionic intermediate **56.3** [100]. Scheme 56 contains only two examples from a large number of compounds prepared in this way. Cyclic CH- acids, phenols, aldehydes or amines were used instead of benzaldehyde and 4-methoxianiline with acceptable yields.



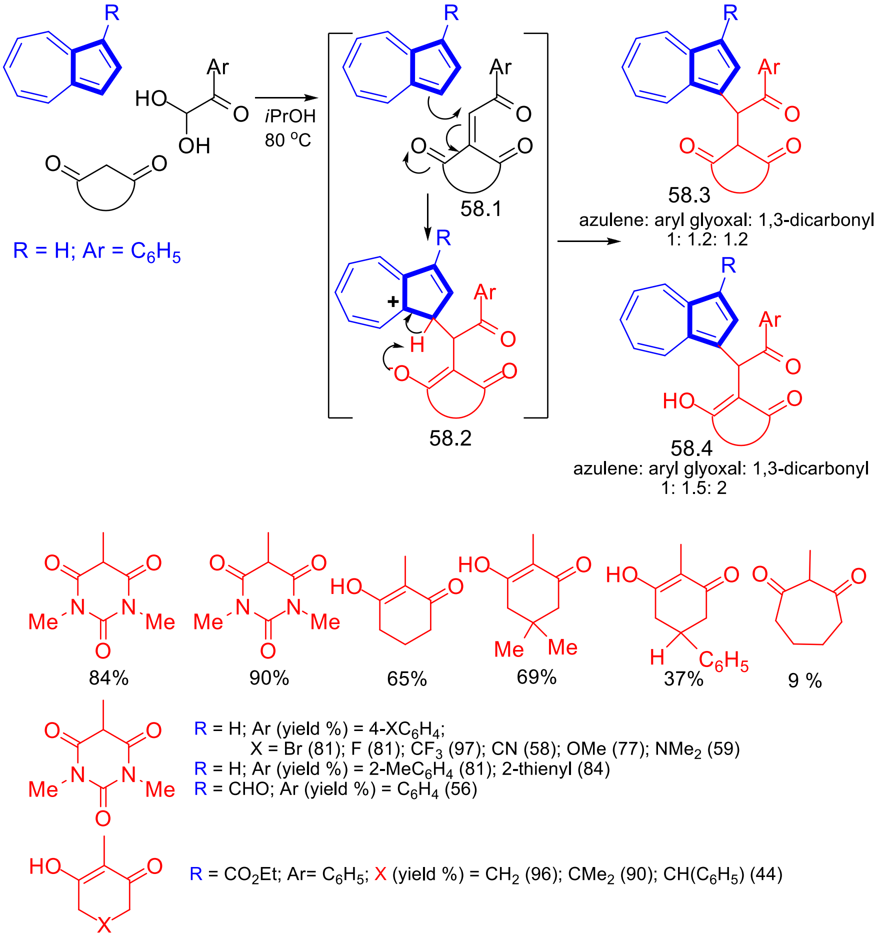
Scheme 56. Guaiazulene–heterocycle hybrid syntheses.

To achieve the 3-(guaiazulen-3-yl)dihydro-1H-indol-4(5H)-ones, **57.1**, with the pyrrolic system included in the molecule, Wang et al. proposed a three-component domino reaction [101]. The reaction starts from guaiazulene, methylglyoxal and enaminones, and takes place with good yield in the presence of acetic acid, as shown in Scheme 57.



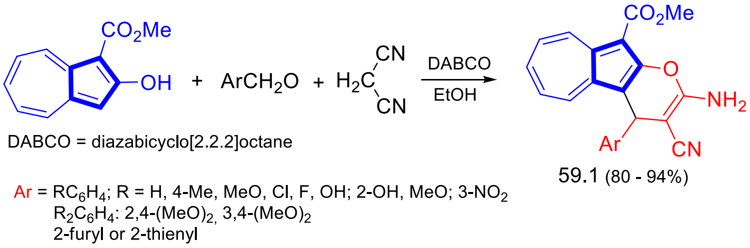
Scheme 57. Three-component domino reaction: guaiazulene + methylglyoxal + enaminones.

The next synthesis starts from the Knoevenagel condensation between aryl glyoxal and a 1,3-dicarbonyl compound, affording intermediate **58.1**. The azulenes present in the reaction medium add to this intermediate, and in the last step a proton transfer in the intermediate **58.2** would produce the desired azulene derivative (Scheme 58) [102]. Depending on the reaction conditions and the structure of the starting materials, diketone **58.3** or ketoenol **58.4** results with the structure and yields described in Scheme 58.



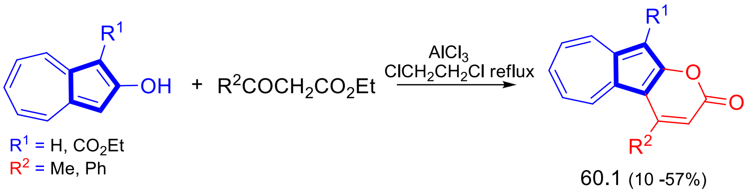
Scheme 58. Reaction of azulenes, aryl glyoxal and 1,3-dicarbonyl compounds.

Much abundant is the literature that describes the obtaining of grafted heterocyclics on azulenes and some examples for the synthesis of such compounds follow to illuminate this subject. The atoms with which azulene is bound to the extra-system are very different, as well as the heteroatoms involved in the grafted system. Thus, at the condensation two atoms belonging to the five-atom ring can participate, one to the five- and the other to the seven-atom ring or both to the seven-atom ring, generating an extra ring with five or six atoms. Atoms such as oxygen, sulfur or nitrogen can be included in the extra-system. A six-atom ring containing an oxygen atom was attached to the five-azulene ring by Wang et al. [103] and Ito et al. [104]. Wang performed a three-component reaction: between ethyl 2-hydroxyazulene-1-carboxylate, aromatic aldehydes, and malononitriles (Scheme 59). A rich range of 2-amino-3-cyano-4-aryl-10-ethoxycarbonylazuleno[2,1-b]pyrans, **59.1**, with varied R substituents was synthesized in this way.



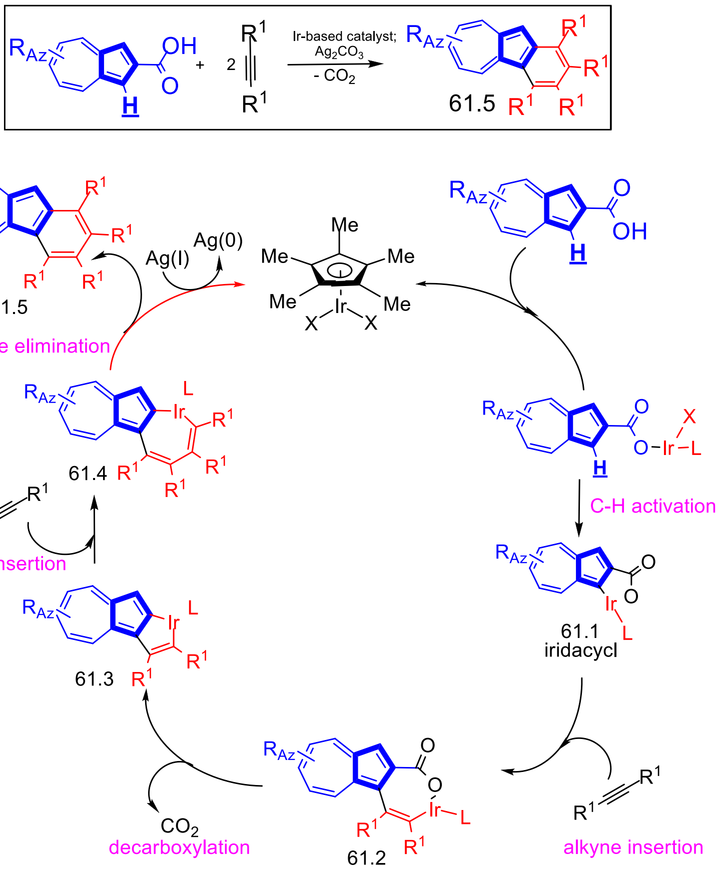
Scheme 59. 2-Amino-3-cyano-4-aryl-10-ethoxycarbonylazuleno[2,1-b]pyrans synthesis.

Somewhat surprising seems to be the Ito condensation of 2-hydroxyazulenes with ethyl acetoacetate or ethyl benzoylacetate (Scheme 60) [103], considering they are rarely used as a catalyst of $AlCl_3$ in other reactions. The yield in the products **60.1** is quite low.



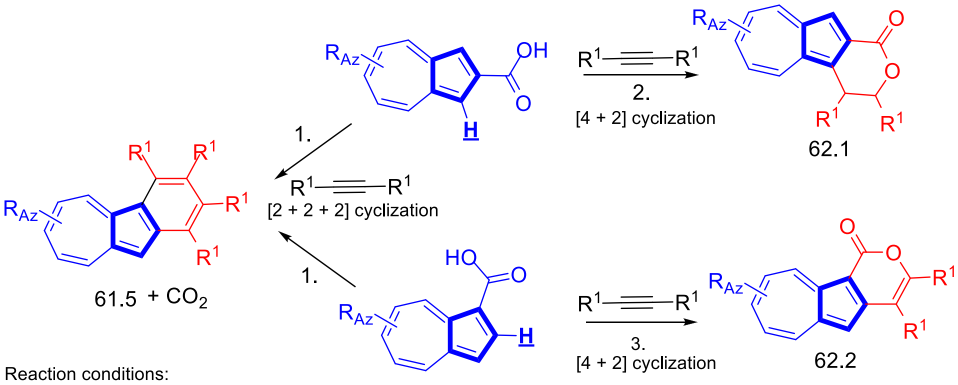
Scheme 60. 1,2-Dihydro-1-oxabenz[a]azulen-2-one derivatives synthesis.

A considerable contribution to the realization of compounds with azulene systems grafted with other rings was brought by the recent works of Maeng et al. In the first paper is described the rhodium- and iridium-catalyzed oxidative [4 + 2] cyclization of azulene carboxylic acids with alkynes (Scheme 61) [105]. After the catalytic activation of C-H bond with formation of iridacycle **61.1** follows the alkyne insertion with the generation of intermediate **61.2**, which is decarboxylated and the new obtained intermediate **61.3** undergoes a new alkyne insertion. The reductive elimination from **61.4** under the influence of Ag(I) leads to the product, tetra(substituted) benzoazulene **61.5**.



Scheme 61. Proposed pathway for synthesis of tetra(substituted) benzoazulene.

In addition to the series of benzoazulenes **61.5**, the authors also synthesized some azulenolactone derivatives, **62.1** and **62.2**. In this case, a Rh-based catalyst replaces the Ir-based catalyst in a [2 + 2 + 2] cyclization reactions of azulenic acids with alkynes. Scheme 62 summarizes aspects related to the conditions in which both series of reactions take place and the yields in which the products are obtained.

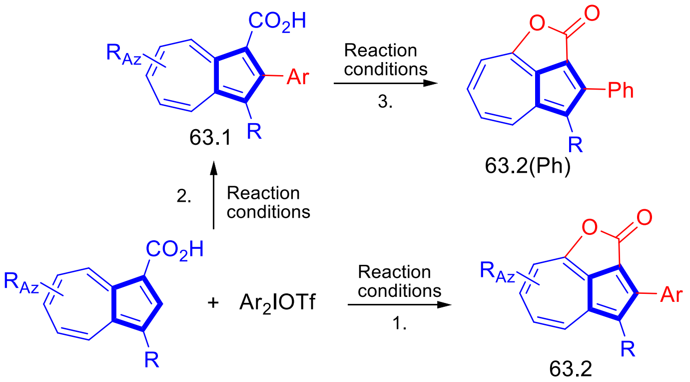


Reaction conditions:
1. $[Cp^*IrCl_2]_2$; Ag_2CO_3; xylene; air
2. $[Cp^*RhCl_2]_2$; Ag_2CO_3; AcOAg; molecular sieve (4 A); DCE; air
3. $[Cp^*RhCl_2]_2$; Ag_2CO_3; K_3PO_4; DMF; air
Cp* = pentamethylcyclopentadienyl

Product; subtituents (average yield in %)
62.1 R_{Az} = H; R^1 = Ph (unsubst. or substituted); 2-thienyl; 3-pyridyl; alkyl (50...83)
62.1 R_{Az} = 6-Me or 6-Ph, 3-Cl R^1 = Ph (unsubst. or substituted) (58...78)
62,2 R_{Az} = H; R^1 = Ph and 3-ClC_6H_4 (40 and 39)
61.5 R_{Az} = H, 6-Me or 6-Ph, 3-Cl; R^1 = Ph (unsubst. or substituted); 2-thienyl (61...86)

Scheme 62. Synthesis of tetra(substituted) benzoazulenes and di(substituted)azulenolactones.

The second target pursued by Maeng was the reaction of azulene 1-carboxylic acid with diaryliodonium salts, and Scheme 63 shows the reaction pathway [106]. The synthesis consists of iridium-catalyzed sequential C(2)-arylation reaction and intramolecular C–O bond formation. Interesting is the intramolecular attack on the seven-atom ring. The reaction can stop at the arylated product in position 2, **63.1**, or it can progress until the formation of 3-arylazulenofuranones, **63.2**. The last product can also be obtained starting from the acid **63.1**.

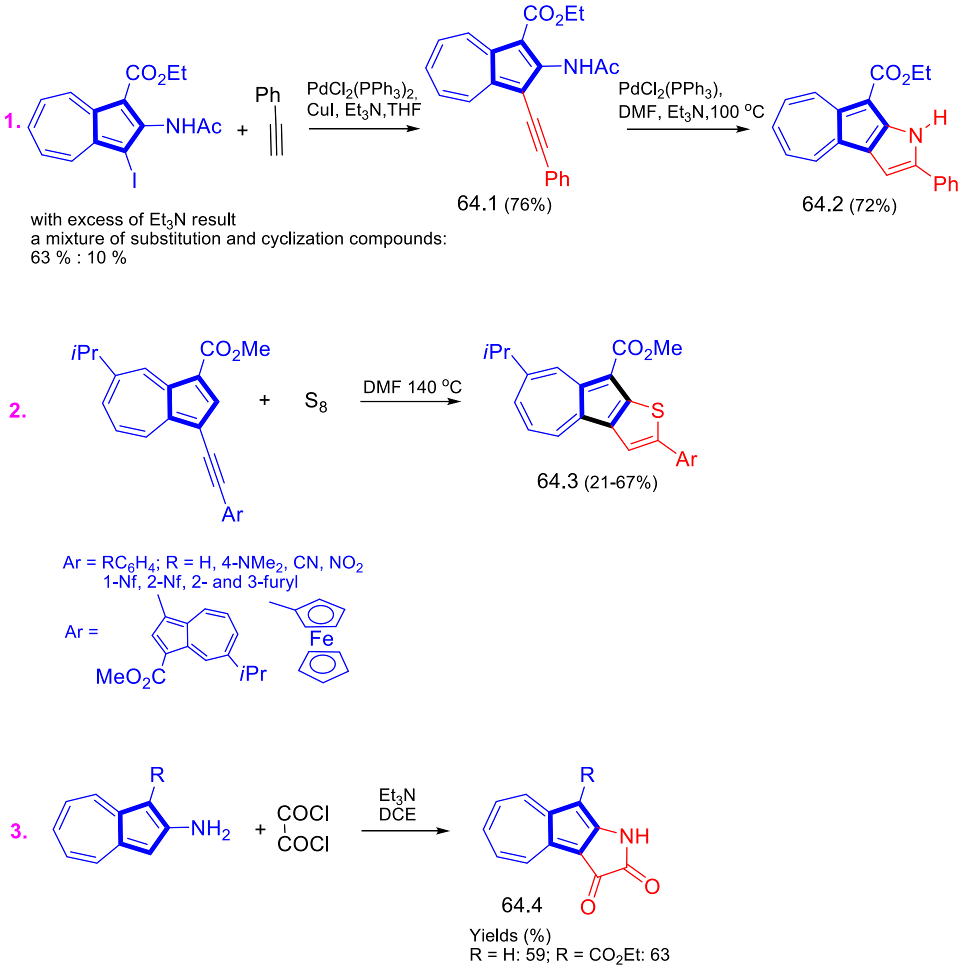


Reaction conditions:
1. $[Cp^*IrCl_2]_2$; I_2; AcOAg; AcOK; DMF/ 80 °C
   for compounds III with Ar = $2\text{-}BrC_6H_4$, Ar_2IBF_4 was used
2. $[Cp^*IrCl_2]_2$; AcOAg; Na_2HPO_4; DMF / 60 °C
3. $[Cp^*IrCl_2]_2$; AcOAg; AcOK; DMF/ 80 °C

Product; subtituents (average yield in %)
63.2 R_{Az} = R = H; Ar = Ph (unsubst. or substituted); 2-thienyl (55...87)
63.2 R_{Az} = 6-Me or 6-Ph, R = H; Ar = Ph (54 or 72)
63.2 R_{Az} = H; R = Me; Ar = Ph (77)
63.1 R_{Az} = R = H; Ar: Ph (unsubst. or substituted); 2-thienyl (68...87)
63.1 R_{Az} = 6-Me or 6-Ph, R = H; Ar = $2\text{-}BrC_6H_4$ (60 or 55)
63.1 R_{Az} = H; R = Me; Ar = $2\text{-}BrC_6H_4$ (53)
63.2(Ph) / 80

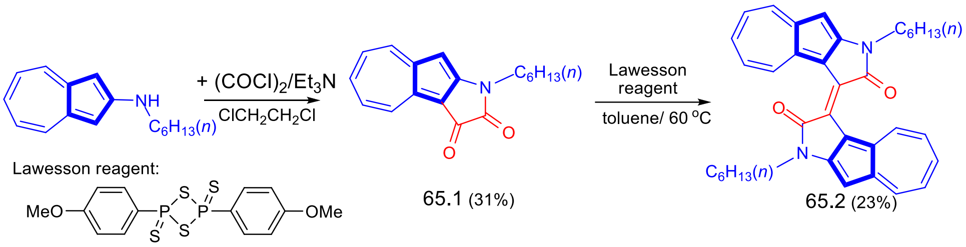
Scheme 63. The arylation of azulene and the synthesis of 3-arylazulenofuranones.

As shown above, apart from the oxygen atom, the literature also includes articles dealing with azulenes grafted with the extra-system containing sulfur or nitrogen. From the large amount of information that has been published, only a few examples are selected that are presented as reactions in Scheme 64 with the specification of the reaction conditions and the yields obtained.



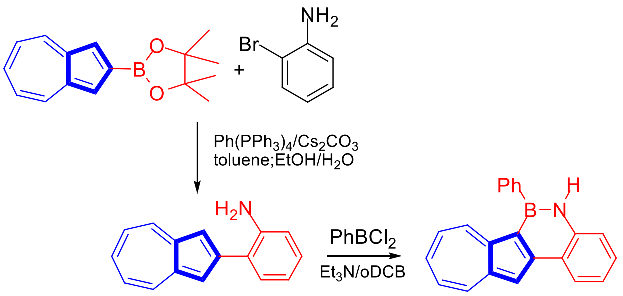
Scheme 64. Synthesis of ethyl 2-phenyl-3H-azuleno[2,1-b]pyrrole-4-carboxylate, **64.2** [107], azuleno[2,1-b]thiophenes, **64.3** [108] and azulene[2,1-b]pyrrole-2,3-dione [109].

In 2022, Gao et al. synthesized an analogue of indigo, continuing the group's series of investigations in the field of π-functionalized materials [110]. Scheme 65 shows the procedure for obtaining intermediate azulenoisatine, **65.**1 and of the separable azulenoisoindigo, **65.2**.



Scheme 65. Synthesis of azulenoisatine, **65.**1 and azulenoisoindigo, **65.2**.

Gao et al. also describes the first synthesis of azulene-based BN-heteroaromatics, building block **66.2**, for synthesizing polycyclic aromatic hydrocarbons [111]. The synthesis occurs through nitrogen-directed aromatic borylation (Scheme 66).



66.1 (74%) 66.2 (65%)

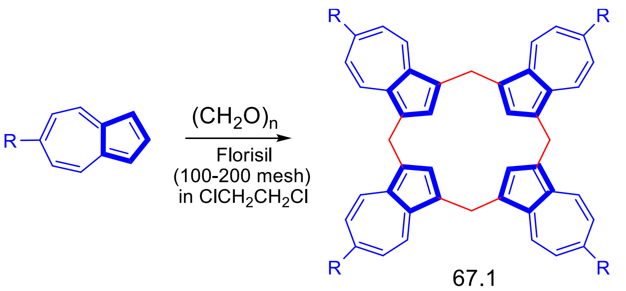
oDCB = o-dichlorobenzene

Scheme 66. Synthesis of azulene-based BN-heteroaromatics.

3.3.5. Calixarene, Azulenophane, and Azuliporphyrin

Many efforts have been focused on the investigation of calixarene, azulenophane and azuliporphyrin, and two reviews have recently appeared regarding this topic [17,21]. Therefore, to complete the information on the behavior of the azulene five ring, only a few examples from these classes of compounds will be given.

The formation of calixarene **67.1** by the reaction of azulenes with formaldehyde in the presence of Florisil (activated magnesium silicate) is illustrated in Scheme 67. The acid-catalyzed reaction affords as major product a polymer with only a low proportion of calixarene [112,113].

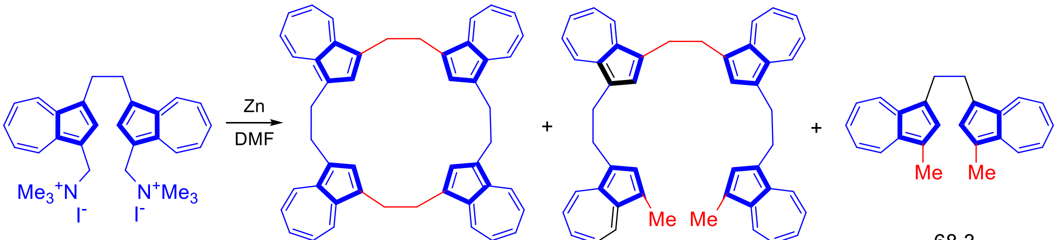


67.1

R; (yield in %): H (74); *t*Bu (68); Me (17); Ph (<10 impure)

Scheme 67. Calixarene synthesis.

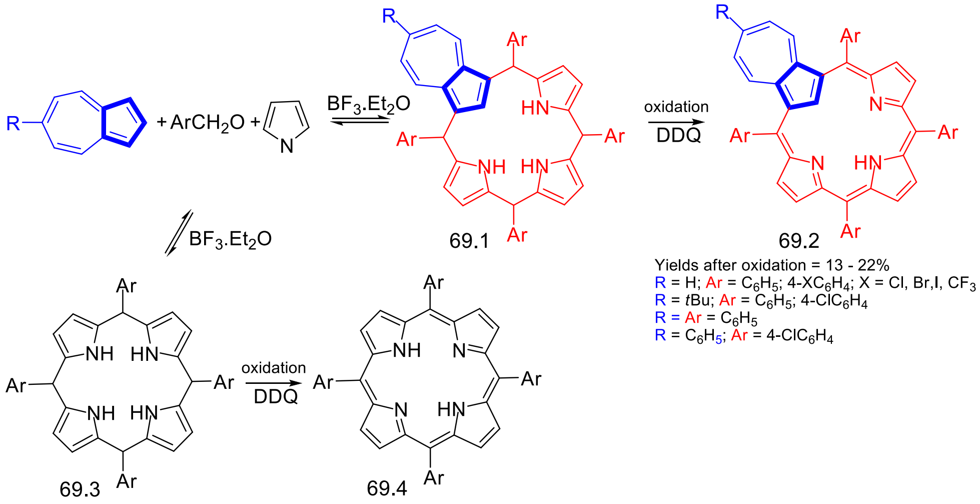
To get to azulenophanes, Fujimura used the route described in Scheme 68 [114]. As can be seen, the reaction mixture is complex and contains, along with azulenophane, **68.1**, the product with the open ring, **68.2**, as well as the dimer **68.1**. It should be noted that very small quantities of products result from the reaction.



68.1 68.2 68.3

Scheme 68. Azulenophane synthesis.

Much wider interest has been in obtaining azuliporphyrines, a special contribution being made by Lash et al. [115,116] and Sprutta et al. [117,118]. One of the many existing procedures for obtaining azuliporphyrines, namely, Rothemund synthesis, exemplified in Scheme 69, affords the desired macrocycles in low yields (~13%) due to the shifted equilibrium in favor of porphyrinogen systems **69.3** and **69.4**. A careful investigation into the structure of azuliporphyrine with two azulene in the porphyrin rings was also carried out by Lash et al. [118,119].



Yields after oxidation = 13 - 22%
R = H; Ar = C_6H_5; 4-XC_6H_4; X = Cl, Br,I, CF_3
R = *t*Bu; Ar = C_6H_5; 4-ClC_6H_4
R = Ar = C_6H_5
R = C_6H_5; Ar = 4-ClC_6H_4

Scheme 69. Lindsey−Rothemund Synthesis of azuliporphyrins.

4. Conclusions

This review proposed a brief presentation of the behavior of the five-membered azulenic ring based on the information from the literature and our results in order to familiarize researchers with the chemistry of this ring. Neither an exhaustive exposition of the synthesis procedures nor a detailed description of them was pursued. It was preferred to introduce reaction schemes that include the reaction conditions and the yields of the obtained products. In this way, the reader can get an idea about the usefulness of the procedures. In a series of cases, the reaction mechanism was briefly discussed in order to allow the researchers' imagination to use the information in possible similar syntheses. The division into chapters took into account reaction conditions and was guided to some extent by the divisions in the published reviews. After the introduction and some considerations about starting azulene, the description of the chemical behavior of azulene was divided into reactions without catalyst and with catalyst. The last chapter summarizes reactions that do not belong to one of the previous series.

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Conflicts of Interest: The author declares no conflicts of interest, financial or otherwise.

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