

Review

# Azulene, Reactivity, and Scientific Interest Inversely Proportional to Ring Size; Part 2: The Seven-Membered Ring

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**Abstract:** The second part of the article *Azulene, Reactivity, and Scientific Interest Inversely Proportional to Ring Size* deals with the chemical behavior of the seven-atom azulenic ring. As the title states, the ability of this system to react is lesser compared to that of the five-atom ring; despite this, a large number of syntheses contain it as a participant in the molecules of starting compounds. This review is focused on certain more frequent syntheses such as nucleophilic substitution of the seven-atom ring or its substituents, vicarious nucleophilic substitutions, substitutions of azulene metallic compounds, or reactions catalyzed by complexes of certain transition metals. The syntheses of tricyclic compounds, porphyrinogenic systems, or azulenocyanines containing an azulenyl moiety are also presented. The adopted presentation is mainly based on reaction schemes that include the reaction conditions, as well as the yields of the products formed.

**Keywords:** azulene; seven-ring reactivity; cross-coupling

## 1. Introduction

The chemical behavior of the azulene five-atom ring was the target of the first part of this review [1]. It was shown there that, unlike naphthalene which is symmetrical with respect to both axes, *x* and *y*, azulene is asymmetric with respect only to the *y* axis (Scheme 1). This creates a difference in electron density between the two azulene rings [2,3] and therefore a remarkable difference between their chemical behavior. The nucleophilicity of the electron-rich five-atom ring promotes the electrophilic character of many azulene reactions. In contrast, the seven-atom ring has an electrophilic character and is expected to prefer nucleophilic reactions. Unfortunately, the charge distribution shows that the electron density at Positions 4(8) and 6 (Scheme 1) does not justify a high ability to react with nucleophilic agents, therefore this kind of reaction will be briefly analyzed at the beginning. Several electrophilic reactions, not specific to seven-atom rings, are also reviewed. Although an appreciable number of reactions take place at the substituents of the seven-atom ring, only a few will be presented in a separate chapter dedicated to this subject. However, special attention will be paid to the reactions catalyzed by complexes of transitional metals, mainly for cross-coupling reactions which are likely to occupy the most important place in the chemistry of the seven-atom ring both from a scientific and a practical point of view. Other chapters describe the syntheses of certain tricyclic compounds containing azulene in the skeleton or of certain substituted azulenes with carbon–carbon triple bonds. Despite the fact that a large amount of information about azulene chemistry can be found in the chapter edited by Zeller in the Houben Weyl Encyclopedia published in 1984 [4], it was considered necessary to exemplify in this review certain synthesis procedures elaborated earlier not only from a historical point of view but also to give fluency to the exposed material.



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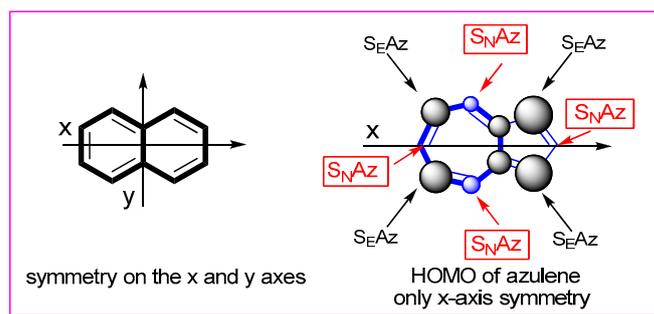
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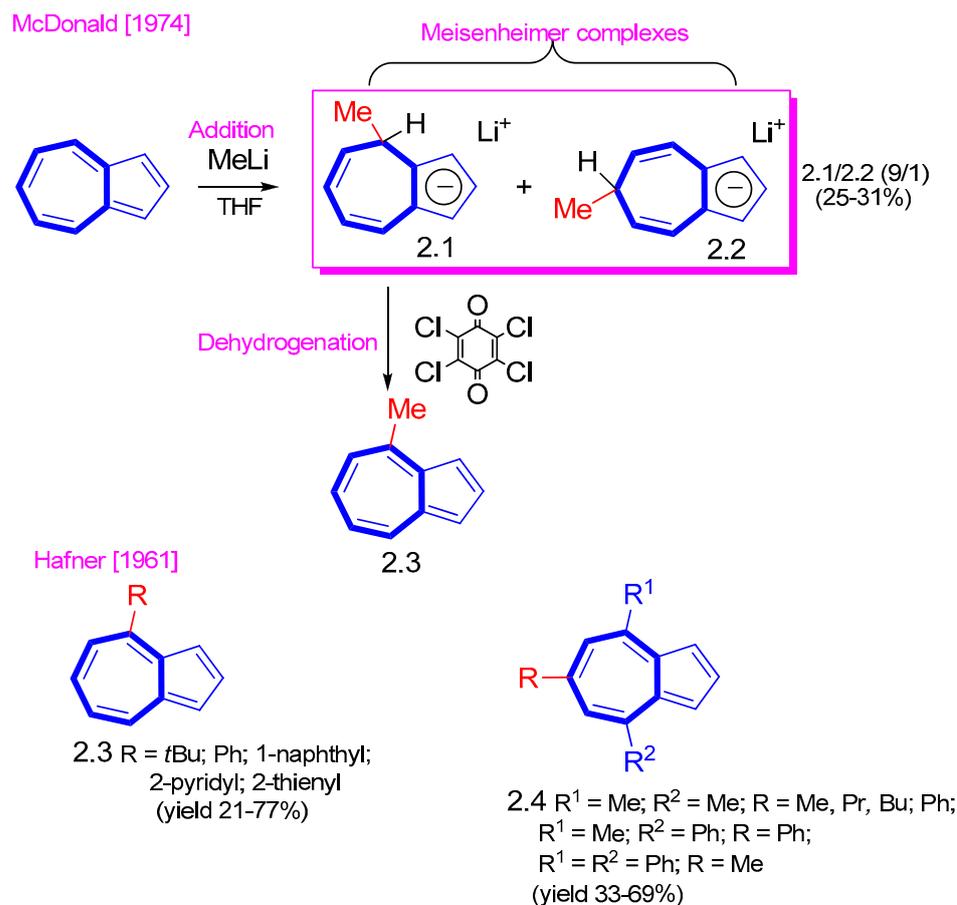
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**Scheme 1.** Symmetry axes of naphthalene and HOMO of azulene.

## 2. Nucleophilic Reactions at Azulene Moiety, $S_NAz$

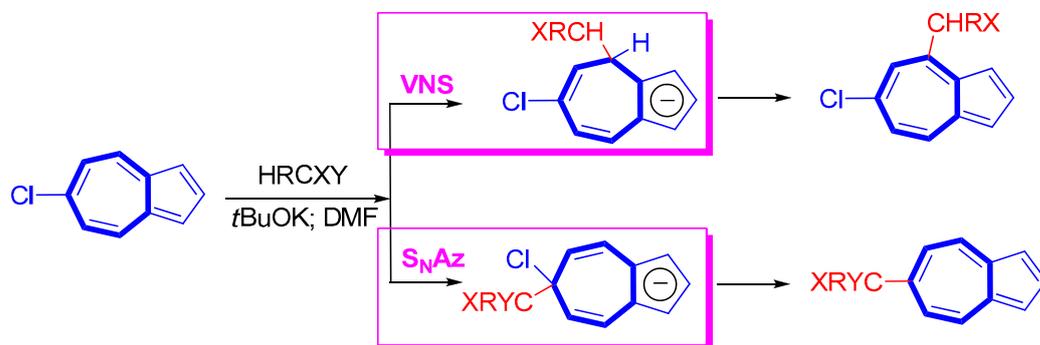
The strong nucleophilic reagent MeLi produces, as the first step, the Meisenheimer complexes **2.1** and **2.2** by addition of a methyl anion to the double bonds of the seven-ring as described in Scheme 2. This process is favored by the involvement of the cyclopentadienyl aromatic system which stabilizes to a certain extent the formed intermediates **2.1** and **2.2**; the subsequent dehydrogenation generates the alkylated azulene. Hafner reported only the formation of the complex **2.1** with methyl in Position 2(4) and the product **2.3** [5], while McDonald obtained both Meisenheimer isomers (ratio **2.1**:**2.2** = 9:1) without being able to obtain the 6-methylated azulene [6,7].



**Scheme 2.** Nucleophile addition to azulene and dehydrogenation of the Meisenheimer complex.

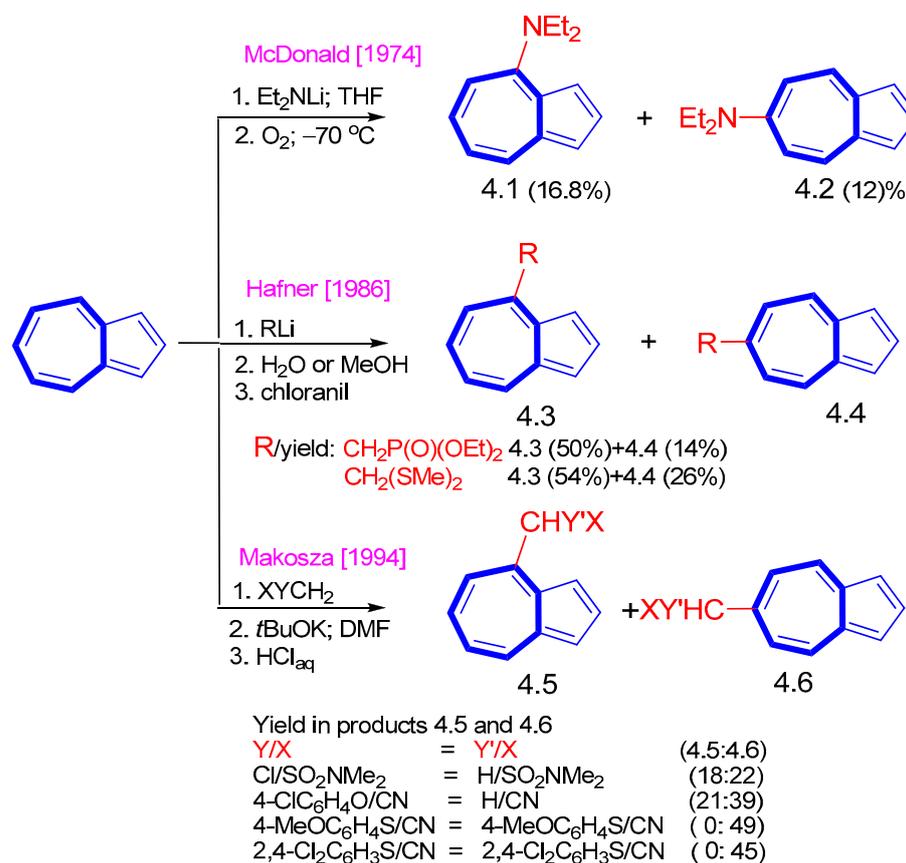
More recently, Makosza paid attention to other nucleophilic substitutions which proceed via an addition- $\beta$ -elimination mechanism which was classified as a vicarious nucleophilic substitution (VNS). The difference between this procedure and the classic

nucleophilic substitution,  $S_NAz$ , results from Scheme 3 [8]. The VSN reagent contains a leaving group, a carbanion stabilizing group, as well as the substituent.



**Scheme 3.** Difference between the vicarious nucleophilic substitution (VNS) and a classical one,  $S_NAz$ .

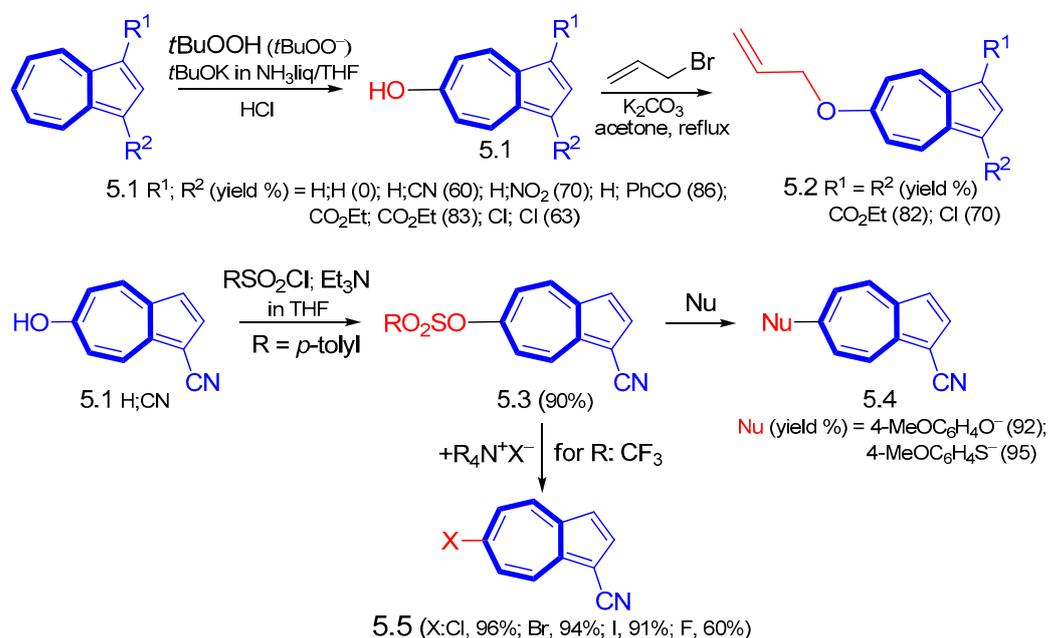
Scheme 4 presents certain additional nucleophilic substitutions reported by Hafner [9], McDonald [6], and Makosza [8].



**Scheme 4.** Certain azulene seven ring substitutions,  $S_NAz$ .

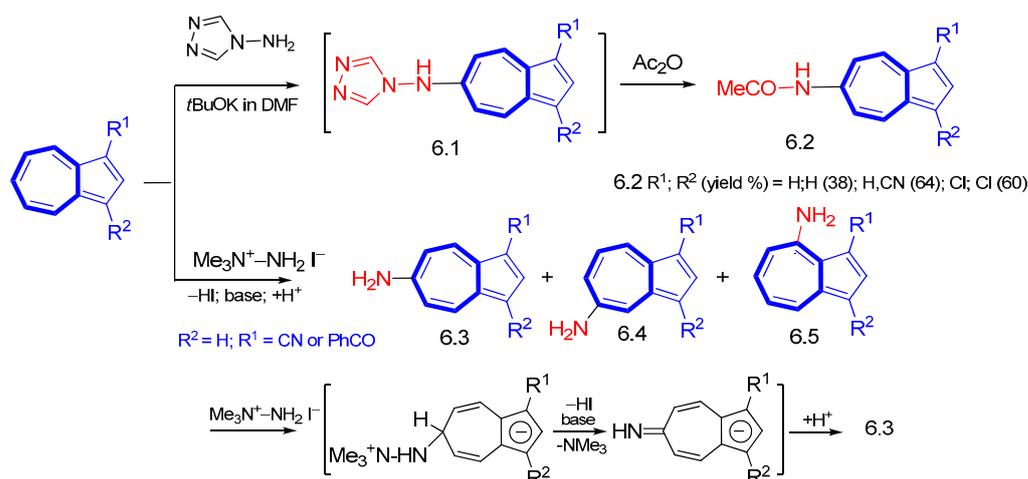
Continuing the interest in the VSN reaction, Makosza investigated the reactions of azulenes' hydroxylation and amination (Scheme 5) [10]. The moderate electrophilicity of azulene was increased by the presence of electron-withdrawing substituents in the five-membered ring. This allowed the formation of a  $\sigma^H$  adduct (the first VSN step) in a concentration sufficiently high for the  $\beta$ -elimination. As a result,  $tBuOO^-$ , a weak nucleophile, reacts efficiently with good yields with these compounds, affording the 6-hydroxyazulene 5.1, while the parent azulene remains inert. As can be seen from

Scheme 5, the 6-hydroxyazulenes acted as raw materials for the synthesis of other interesting compounds, 5.2–5.5.



**Scheme 5.** Hydroxylation of azulenes in Position 6.

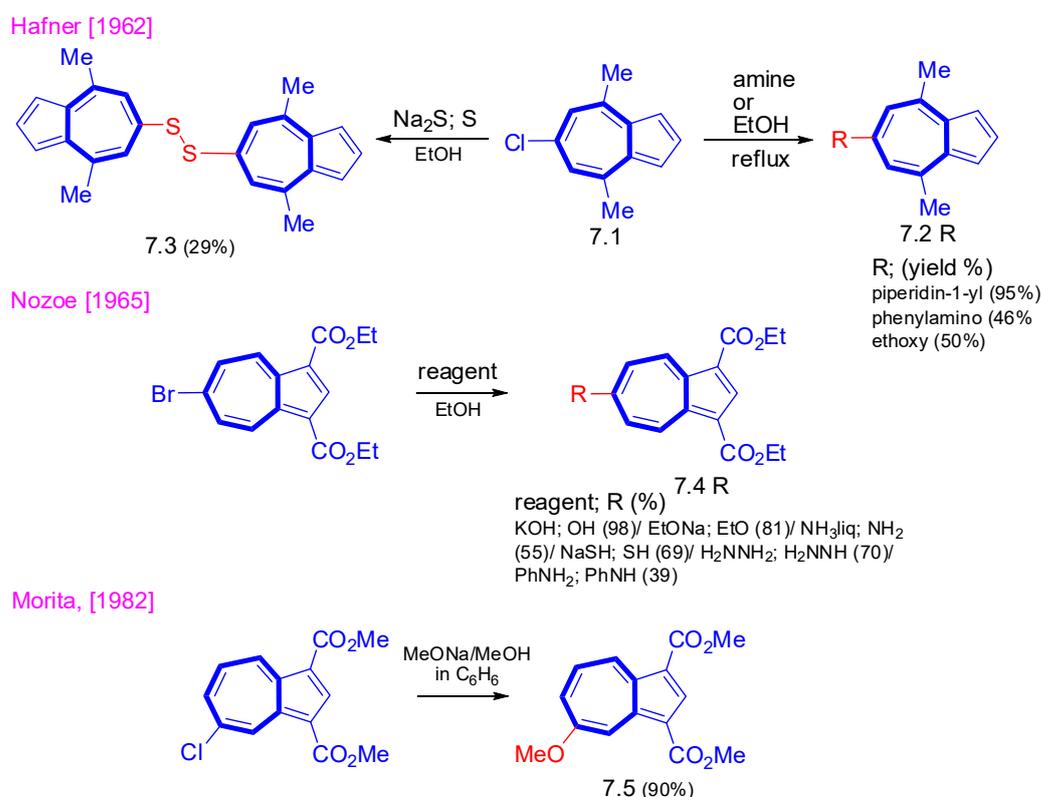
Makosza also achieved the amination of azulenes in Position 6 using 4-amino-1,2,4-triazole as described in Scheme 6 [10]. The 6-aminoazulenes had a moderate stability, thus they were isolated, purified, and characterized as the corresponding acetyl derivatives, 6.2. Vicarious nucleophilic substitution of hydrogen was also performed using *N,N,N*-trimethylhydrazinium iodide for further electrophilic azulene derivatives [11] and the proposed mechanism in this case is presented in Scheme 6 (for Position 6).



**Scheme 6.** Amination of azulenes in Position 6 (procedure for VSN).

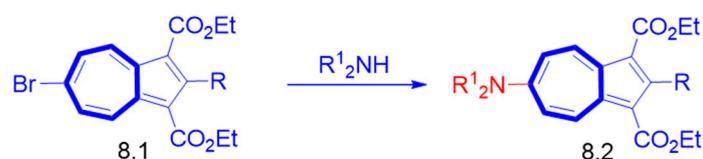
A consistent subchapter was dedicated by Zeller in the Houben Weyl Encyclopedia [4] to the substitution S<sub>N</sub>Az of certain atoms or groups present on the seven-atom ring. Certain examples will be repeated below and completed with more recent syntheses. The classical nucleophilic substitution, S<sub>N</sub>Az, of the halogen in Position 6 of azulene was studied by Hafner et al. [12] and Nozoe et al. [13], and certain syntheses are shown in Scheme 7. An interesting reaction is that obtaining 2-bis(4,8-dimethylazulene-6-yl)disulfane, 7.3, starting from 6-chloro-4,8-dimethylazulene, 7.1, Na<sub>2</sub>S, and sulfur. The substitution proposed by

Nozoe or Morita [14] starts from the 1,3-disubstituted compound with the withdrawing group  $\text{CO}_2\text{R}$  and occurs with a wide variety of reagents with good to moderate yields.



**Scheme 7.** Several nucleophilic early azulene substitutions,  $\text{S}_{\text{N}}\text{Az}$ .

A contribution to the investigation of nucleophilic amination of azulenes  $\text{S}_{\text{N}}\text{Az}$  in Position 6 by replacing Br came from Soji et al. in two papers. In these syntheses, azulenes without a substituent in Position 2, **8.1**(R: H) [15], or with  $\text{NH}_2$  in this position, **8.1**(R:  $\text{NH}_2$ ) [16], were reacted with various cyclic amines (Scheme 8). The reaction occurred in relatively severe experimental conditions. After protecting the amino group in Position 2, **8.1**(R:  $\text{NHCOCF}_3$ ), the reaction proceeded at room temperature but the yields were low [16].

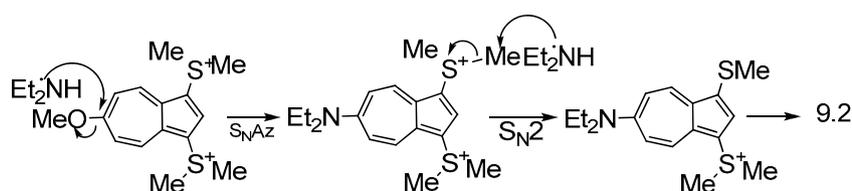
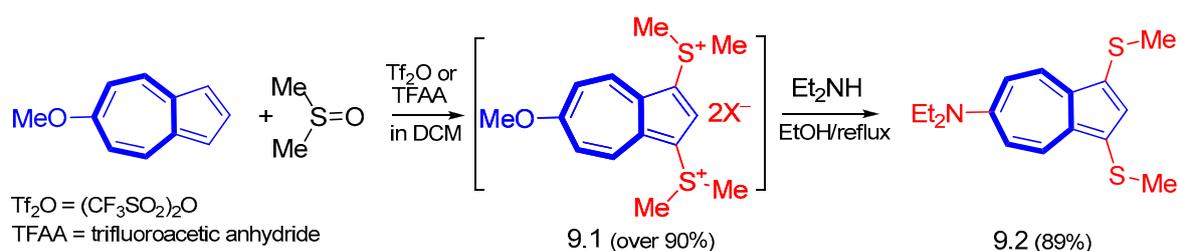


**Soji [2015]** 130 °C; in sealed tube  
R =  $\text{NH}_2$ ;  $\text{R}^1_2\text{NH}$  (yield in %) = pyrrolidine (94), piperidine (89), morpholine (91)  
R =  $\text{NHCOCF}_3$ ; room temp.;  $\text{R}^1_2\text{NH}$  (yield in %) = piperidine (34), morpholine (15)

**Soji [2019]** amine; 80 °C or reflux  
R = H;  $\text{R}^1_2\text{NH}$  (yield in %) = pyrrolidine (95), piperidine (96), morpholine (94), N-ethylpiperazine (83), diethylamine (93), *n*-butylamine (71), *t*-butylamine (50),

**Scheme 8.** Amination of azulenes in Position 6 (procedure for  $\text{S}_{\text{N}}\text{Az}$ ).

As already mentioned, a series of electron-withdrawing substituents (e.g.,  $\text{CO}_2\text{R}$ , COR, CN, etc.) in Positions 1 and 3 favors both types of nucleophilic substitution:  $\text{S}_{\text{N}}\text{Az}$  and VSN. As show Scheme 9, the high reactivity owing to the electron-withdrawing sulfonium ions at these positions (in compound **9.1**) allows the amination of  $\text{S}_{\text{N}}\text{Az}$  with excellent yields [17]. The reaction continues to the product **9.2** by nucleophilic substitution ( $\text{S}_{\text{N}}2$ ) at the substituents in Positions 1 and 3 as proposed in the mechanism described in Scheme 9.

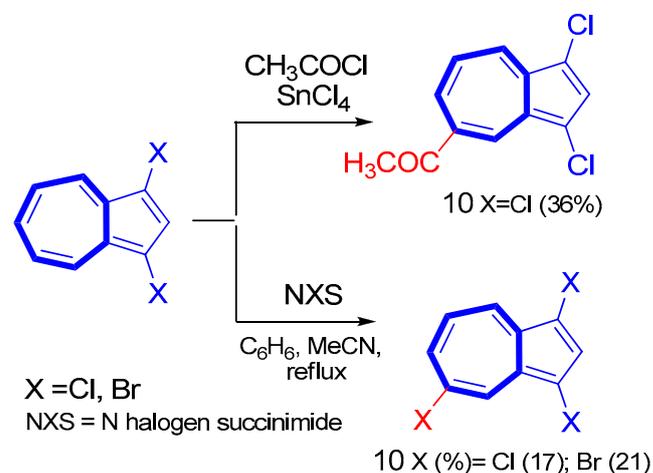


Scheme 9.  $\text{S}_{\text{N}}\text{Az}$  of the MeO group in Position 6 with  $\text{Et}_2\text{N}$ .

### 3. Electrophilic Substitutions at Azulene Moiety, $\text{S}_{\text{E}}\text{Az}$

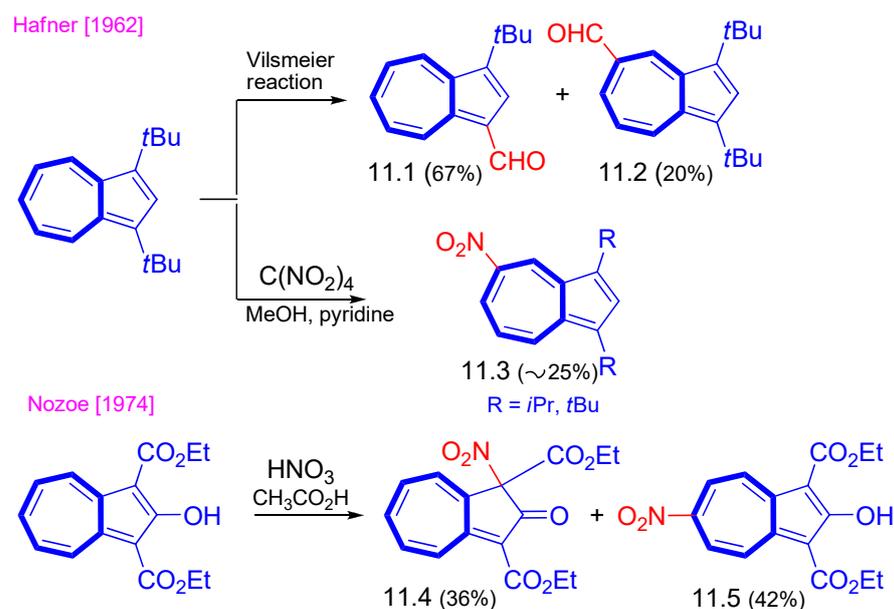
As follows from Scheme 1, the azulene electrophilic substitution,  $\text{S}_{\text{E}}\text{Az}$ , is not characteristic for the seven-atom ring of azulene. Positions 1 and 3 are by far the most favored in this regard. This is why electrophilic attack takes place on seven-membered ring only when these two positions are occupied and the electrophilic agents have an increased effectiveness. These arguments are in support of the low importance given to this type of reaction over time. A few examples of  $\text{S}_{\text{E}}\text{Az}$  for edification will still be cited in the following.

With Positions 1 and 3 blocked with halogen atoms, Anderson and Repolge achieved azulene substitution in Position 5 with both acetyl [18] and halogen [19] under the classical electrophile procedure (Scheme 10).



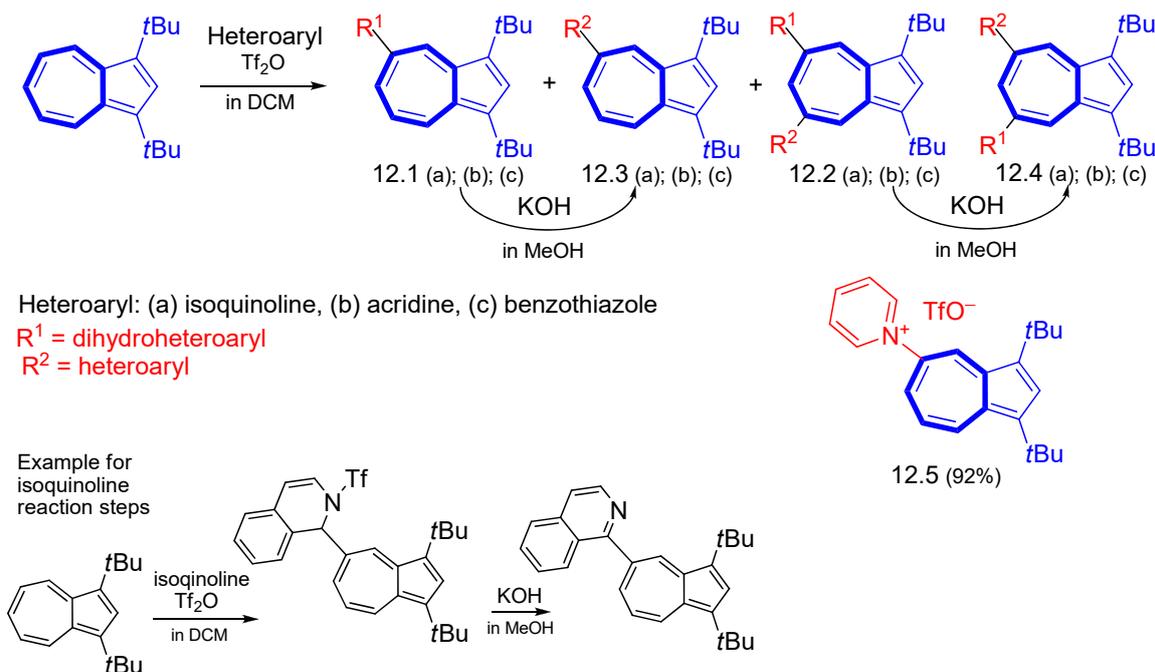
Scheme 10. Electrophilic halogenation and acylation of the azulene seven ring,  $\text{S}_{\text{E}}\text{Az}$ .

Hafner [20] and Nozoe [21] were also concerned with the possibility of  $\text{S}_{\text{E}}\text{Az}$  reactions at the seven ring (Scheme 11). For the Vilsmeier reaction and nitration, the first cited author used 1,3-dialkylated azulene. The Vilsmeier reaction gave the compound **11.2** after  $\text{S}_{\text{E}}\text{Az}$  in Position 7 and the compound **11.1** by the electrophile substitution of one *t*Bu group. Nitration of diethyl 2-hydroxyazulene-1,3-dicarboxylate occurred, obtaining diethyl 1-nitro-2-oxo-1,2-dihydroazulene-1,3-dicarboxylate, **11.4**; the  $\text{S}_{\text{E}}\text{Az}$  product **11.5** was also formed in high amounts.



**Scheme 11.** Vilsmeier reaction and azulene nitration.

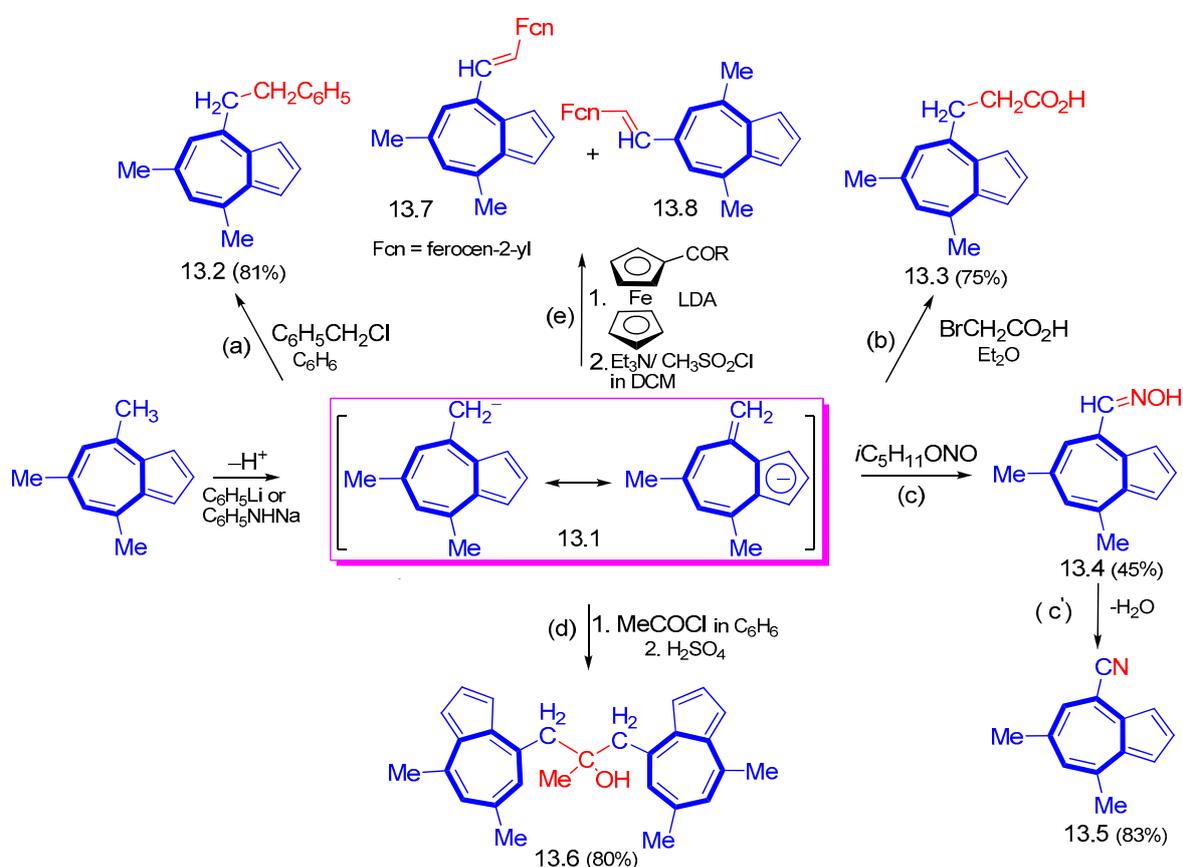
More recently, Shoji et al. obtained N-containing heteroarylazulenes by the electrophilic substitution of 1,3-di-*tert*-butylazulene [22] without the presence of a transition metal catalyst. The triflates of several N-containing heterocycles were used as reagents, and the results are included in Scheme 12. As intermediates, dihydroheteroarylazulenes **12.1** and **12.2** were formed. The reaction mixture can contain mono- and di-substituted compounds, **12.3** and **12.4**, and also the intermediate widely depending on the ratio between azulene, Tf<sub>2</sub>O, and heteroaryl. The intermediates were also obtained by reaction under milder reaction conditions and can be aromatized in the presence of KOH in ethanol. All reactions proceeded with very good yields. When pyridine was used as a starting material, the pyridinium compound **12.5** resulted as the only product (yield: 92%).



**Scheme 12.** Synthesis of N-containing heteroarylazulenes by electrophilic substitution.

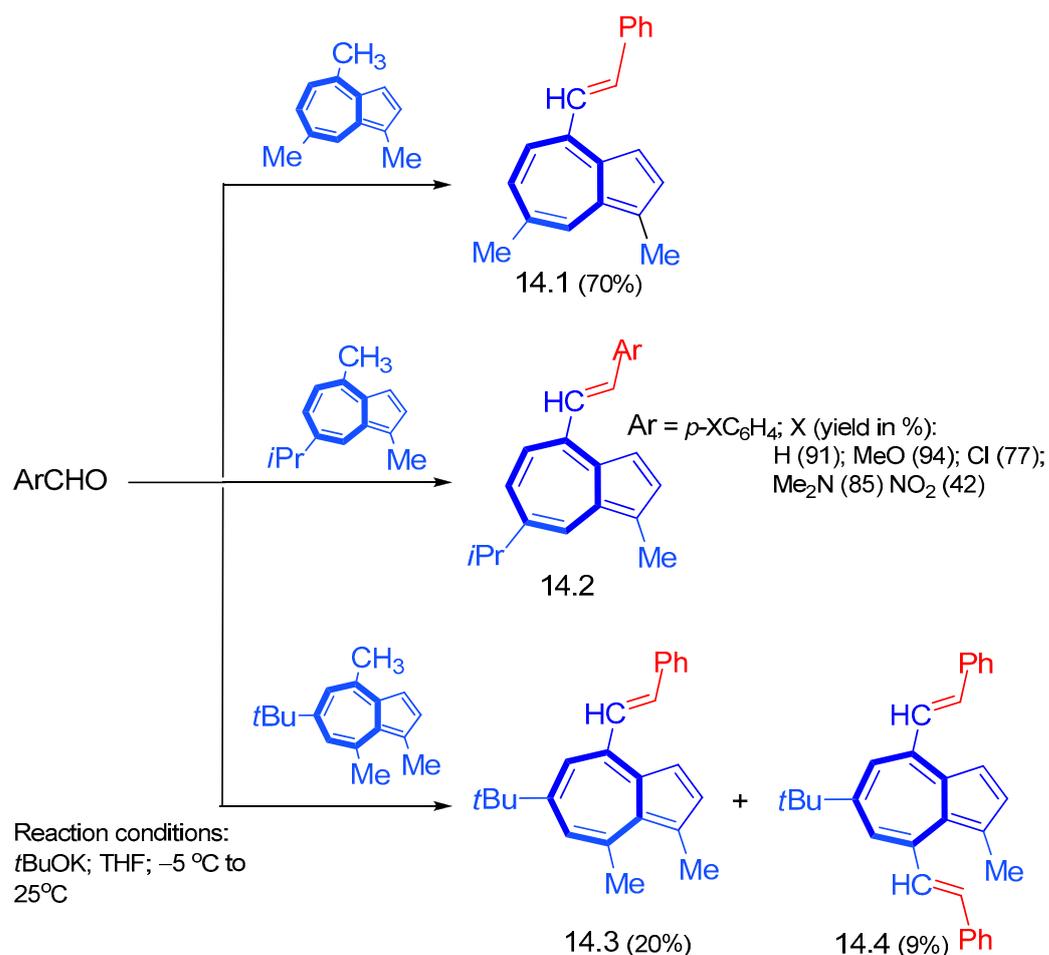
#### 4. Nucleophilic Reactions at Azulene Substituents

Contrary to the low interest towards  $S_NAz$ , nucleophilic reactions involving azulenic substituents have been studied frequently and with increasing interest. Many of these have concerned the nucleophilic substitution of a hydrogen atom belonging to an alkyl group in Position 4(6). Examining Scheme 13, it is obvious that this nucleophilic reaction takes place in the first step by the elimination of a proton with the development of the cyclopentadienyl aromatic system that stabilizes the intermediate, anion **13.1**, and promotes the reaction. The scheme exemplifies a series of such reactions which, despite being carried out before 2000, can create a comprehensive view about the reaction. Thus, the halogenated reagents were used in Reactions (a) [23] and (b) [24] and, with *iso*-pentyl nitrite, the oxime **13.4** was obtained (route (c)) which was subsequently used for the generation of the nitrile **13.5** (route (c')) [25]. The attempt to acylate trimethylazulene led to the condensation product **13.6** in a high yield [23]. Herrmann et al. condensed the trimethylazulene with ferrocen-2-yl ketones in order to prepare compounds with NLO potential, **13.7** and **13.8**. The reaction occurred at methyls in both Positions 4 and 6 [26,27].



**Scheme 13.** Nucleophilic substitution of hydrogen belonging to the alkyl group in Position 4.

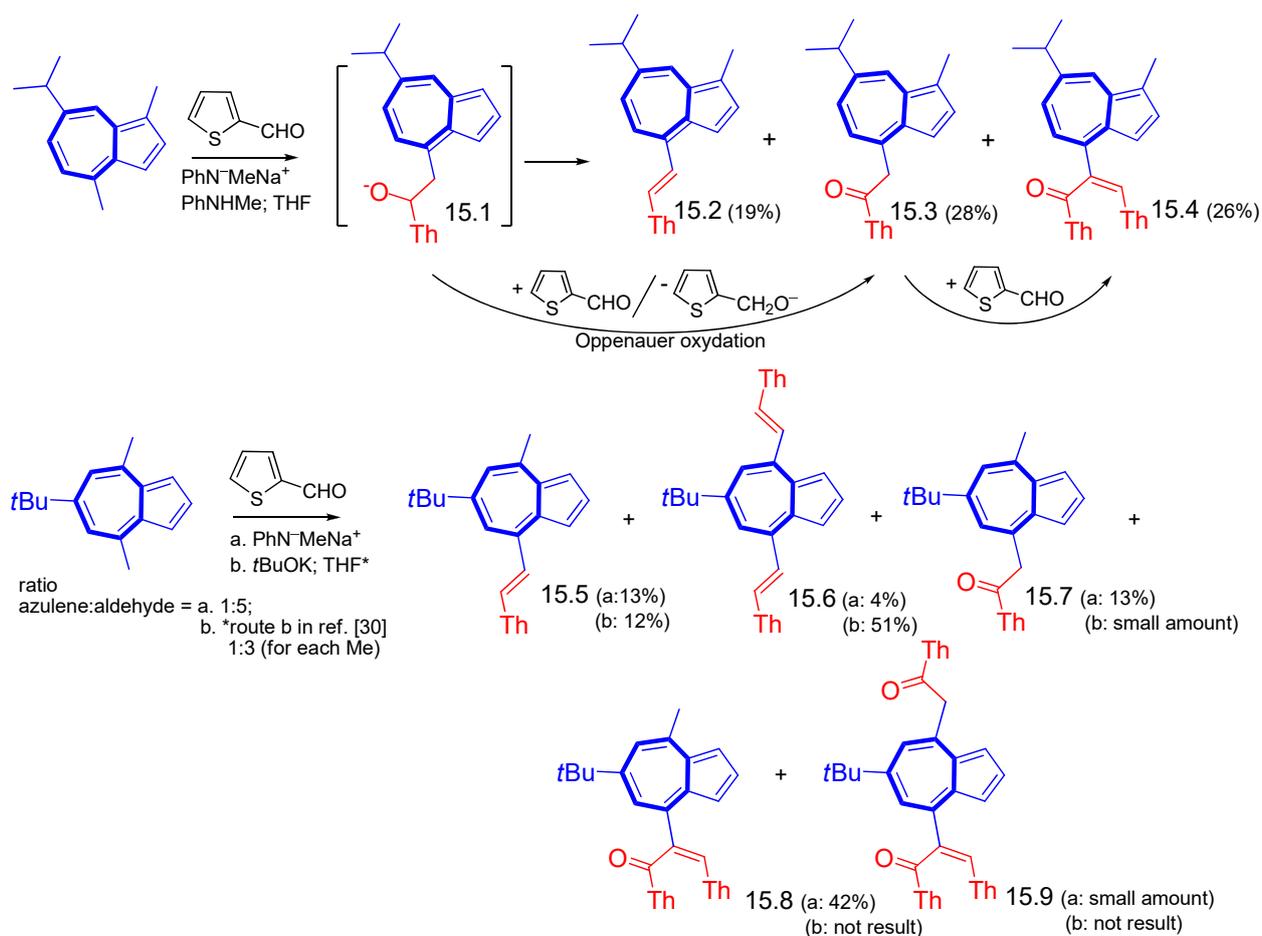
Hansen condensed the methyl group from Position 4 belonging to several polyalkylated azulenes with various benzaldehydes, with the aim of affording styrylazulenes and improving the conditions under which the reaction takes place (Scheme 14) [28]. When both Positions 4 and 8 were methylated, the condensation took place at both positions (compounds **14.3** and **14.4**). The phenyl substitution with  $\text{NO}_2$  dramatically decreased the yield (compound **14.2**  $\text{NO}_2$ ), as well as the substitution near the bulky *t*Bu group (compounds **14.3** and **14.4**).



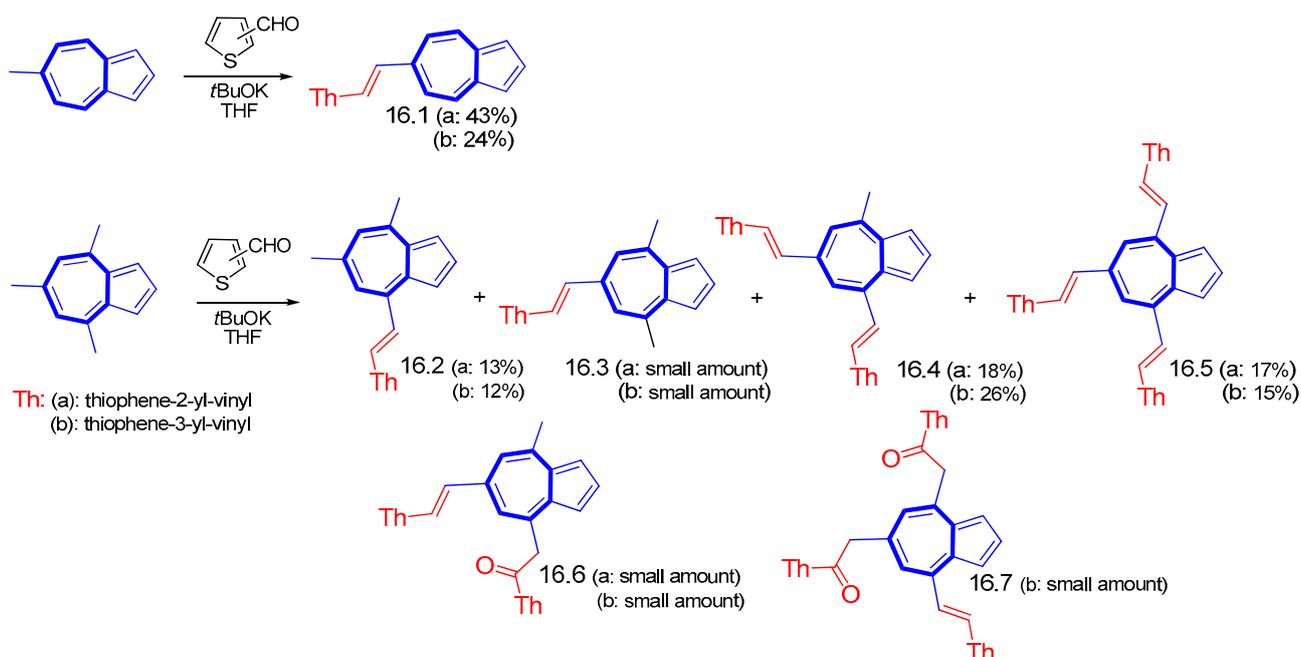
**Scheme 14.** Synthesis of 4-stirylazulenes.

In 2008, Razus et al. published preliminary results obtained by the condensation of the methyl groups belonging to the seven-membered ring with thiophene-2-carbaldehyde in the presence of sodium *N*-methylanilide (Scheme 15) [29]. The resultant mixture was complex, containing a reduced amount of the attempted vinylazulene **15.2**. In more significant quantities, the ketone **15.3** resulted, an Oppenauer oxidation product of the intermediate alkoxide **15.1** with the used excess of starting aldehyde. Another condensation product between the ketone **15.3** and thiophene aldehyde, the compound **15.4**, was present. Starting from 4,8-dimethyl-6-*tert*-butylazulene, the change in the base could be observed. Using PhNMeNa, a high amount of the secondary condensation compounds **15.7** and **15.8** prevailed compared to styryl derivatives such as **15.5** and **15.6**. With *t*BuOK [30], together with a small amount of the ketone **15.7**, mainly vinyl compounds such as **15.5** and **15.6** were generated. The compound **15.9** was also detected by LC-MS analysis.

This investigation was continued in 2020 [30] by the condensation of 6-methylazulene, 4,8-dimethyl-6-*tert*-butylazulene, and 4,6,8-trimethylazulene with thiophene 2- and 3-carbaldehyde using *t*BuOK as a base. The reaction of guaiazulene is presented in Scheme 15 in comparison with the reaction promoted by the sodium *N*-methylanilide. The reaction in the presence of alkoxide proceeded towards vinyl products and the ketone resulted only in very small quantities. This trend was also maintained when started from 6-methylazulene or from 4,6,8-trimethylazulene (Scheme 16). The 6-methylazulene reacted with thiophene carbaldehydes, giving exclusively vinyl derivatives: **16.1**. The reaction mixture obtained after the reaction of trimethylazulene contains mono, bis, and tris-vinyl azulene, **16.2** to **16.5**, in moderate yields and very small amounts from ketone derivatives such as **16.6** and **16.7** which were only detected by LC-MS analysis. The obtained results show a similarity in the behavior of the two thiophene aldehydes used in the reactions.



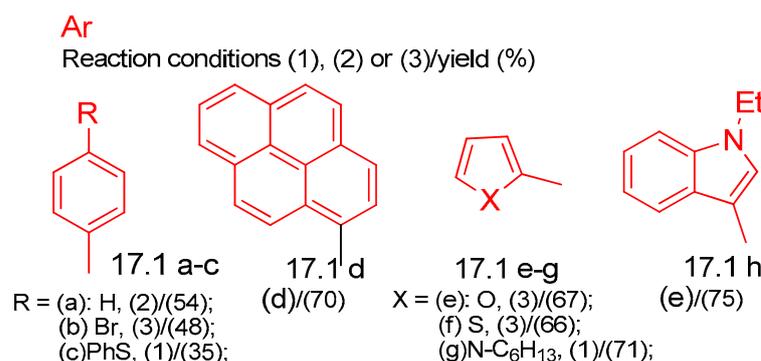
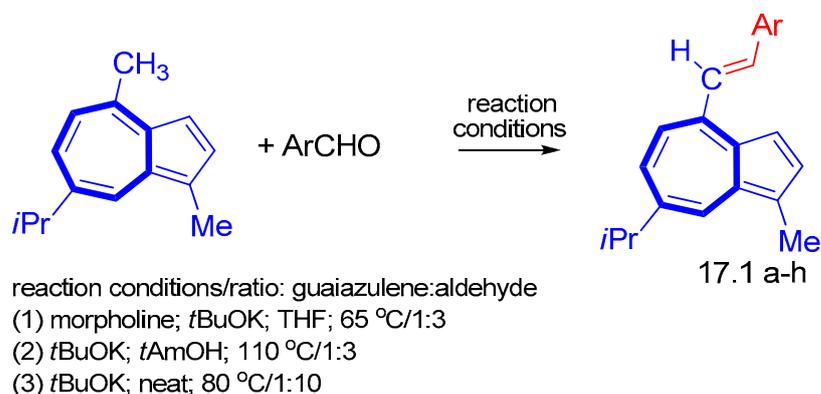
Scheme 15. Condensation of guaiazulene with thiophene-2-carbaldehyde.



Scheme 16. Condensation of guaiazulene with thiophene 2- and 3-carbaldehyde.

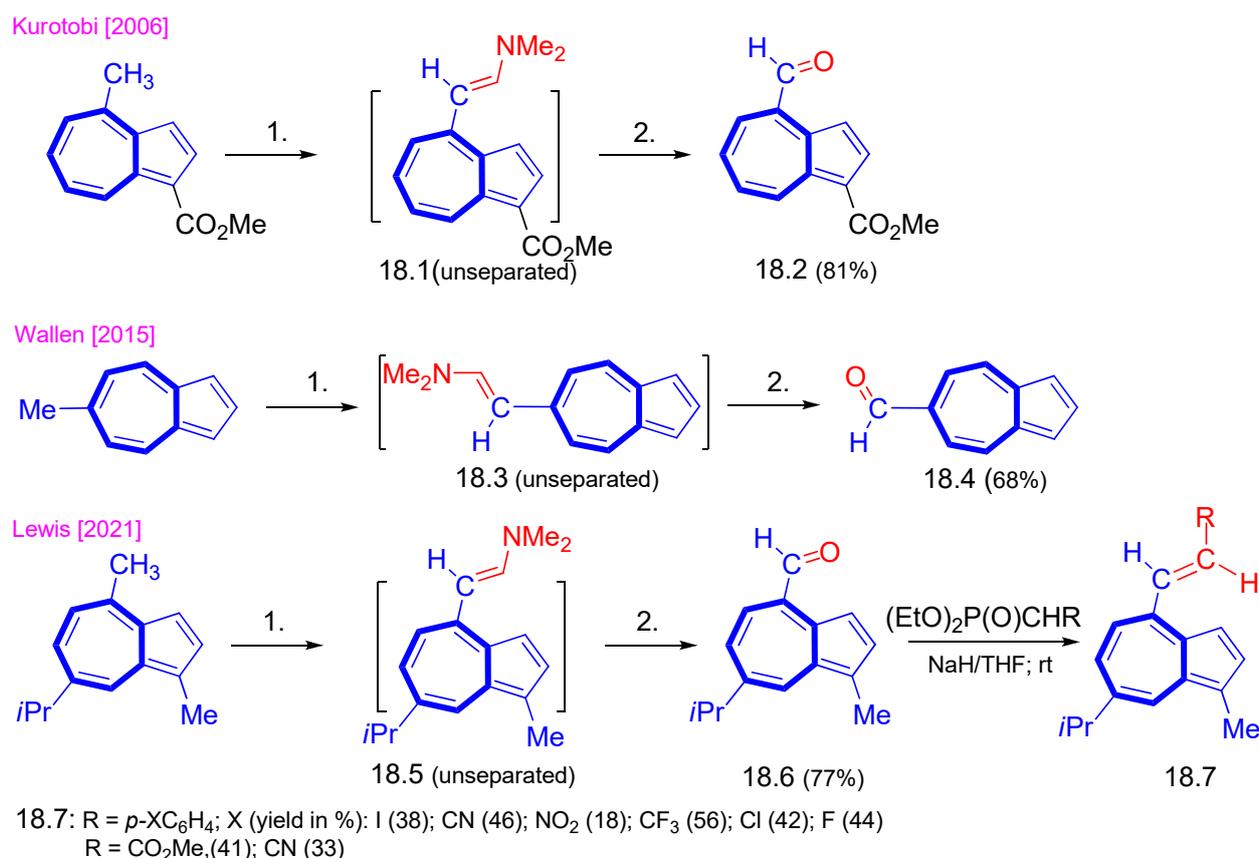
During a study dealing with chromophoric materials derived from guaiazulene, Belfield et al. [31] condensed certain aromatic and heteroaromatic aldehydes with guaiazu-

lene. As presented in Scheme 17, several sets of reaction conditions were tried, various aldehydes served as raw materials, and the yields were between modest and good. It should be noted that, after changing the reaction conditions (*t*BuOK; neat) [31] compared to the previous ones (PhNMeNa; THF) [29], the results for the condensation of thiophene-2-aldehyde were very different. Thus, in the presence of alkoxide/neat, the only reaction product is the alkene (17.1f = 15.2) and the formation of ketones was not observed despite the excess of aldehyde used.



**Scheme 17.** Condensation of guaiazulene with certain aromatic and heteroaromatic aldehydes.

The possibility of using azulene carbaldehydes as building blocks for a wide range of syntheses has boosted investigations in this direction. Vilsmeier formylation of the azulene five-membered ring by reaction with dialkylacylamides in the presence of POCl<sub>3</sub> was extensively presented in Zeller's review [4] and is still frequently used to obtain azulene compounds. The same cannot be said about the azulene carbaldehydes with the CHO group at the seven-membered ring. As such, interest in obtaining these azulene compounds has been present in the last decades and, in Scheme 18, certain syntheses proposed for this purpose are presented together with a few examples of vinylazulenes obtained starting from the azulene carbaldehyde. The synthesis proposed by Kurotobi et al. [32] started from 4-methylazulene substituted with the electron-withdrawing group CO<sub>2</sub>Me in Position 1. This reacted with N,N-dimethylformamide dimethyl acetal giving the enamine intermediate 18.1 which was subsequently oxidized to aldehyde 18.2 with NaIO<sub>4</sub>. Wallén et al. obtained the aldehyde 18.4 from methylazulene by the same route [33], and guaiazulene was transformed by Lewis into the aldehyde 18.6 [34] which was alkenylated by a Horner–Wadsworth–Emmons reaction carried out using a variety of phosphonates. Comparing the results obtained by Lewis for the vinylazulene 18.7 (R = Cl or NO<sub>2</sub>) with those for the similar compound 14.2, obtained by the Hansen procedure, the yields of the latter compound were superior.



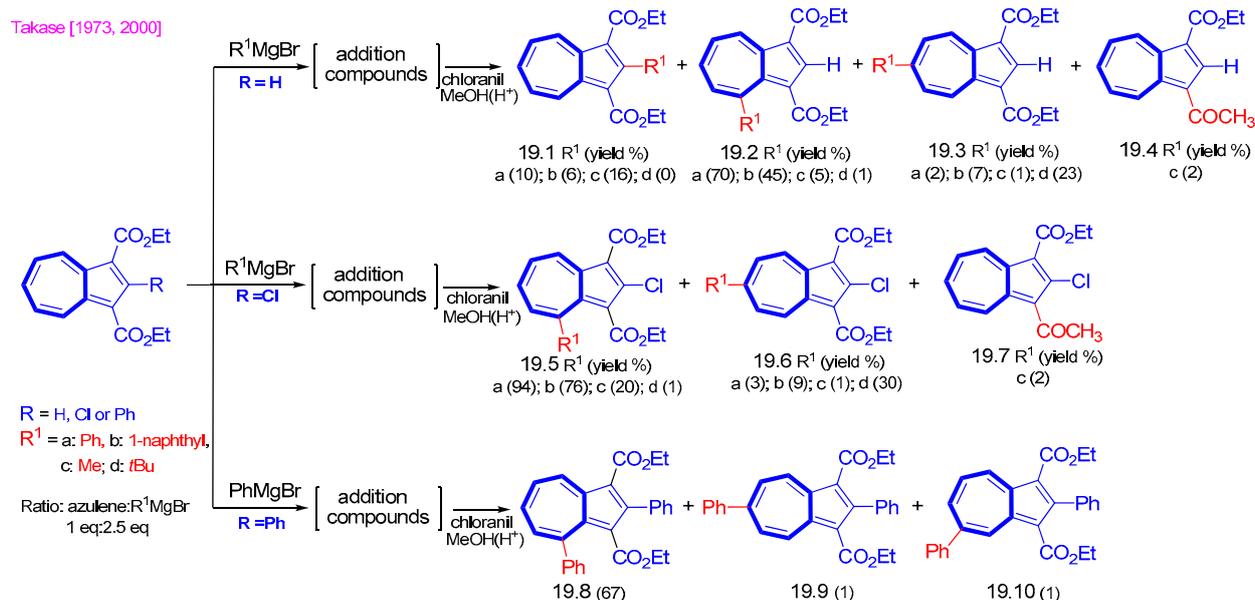
Reaction conditions:

1. (MeO)<sub>2</sub>CHNMe<sub>2</sub>  
DMF at 140 °C
2. NaIO<sub>4</sub>  
THF/H<sub>2</sub>O; rt

**Scheme 18.** Synthesis of enamine intermediates and subsequent corresponding azulene carbaldehydes.

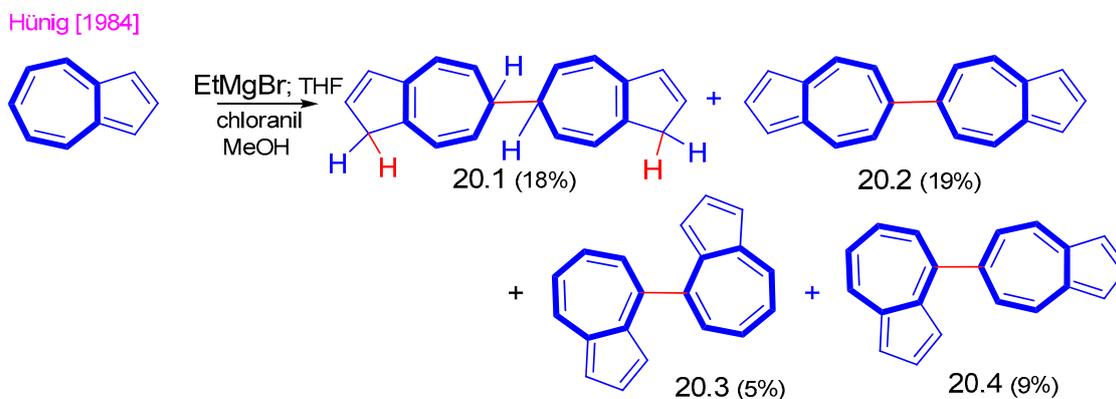
### 5. Reaction with Organometallic Derivatives

Takase et al. reported in 2000 [35] their research, begun in 1973, on the treatment of a series of azulenes with organomagnesium compounds. The reaction occurred in two steps: addition of an organometallic compound and dehydrogenation with chloranil to rebuild the azulenic system (Scheme 19). The authors paid attention to the nature of the organomagnesium derivative but also to the influence of the azulene substituents. Since the addition is nucleophilic, the authors started with the favorable diethyl azulene-1,3-dicarboxylate. Without a substituent in Position 2, this position is attacked in a reduced proportion (compound **19.1a** to **d**), and in the preferred seven-membered ring, Position 4 is activated over Position 6 (compounds **19.2a** to **d** and **19.3a** to **d**, respectively). The bulkiness of the agents affects the positions of the azulene attack; thus, the substitution with *t*Bu preferred Position 6 (compounds **19.3d**). The chlorine in Position 2 was not sensitive to the presence of the Grignard compounds, and the ratio between the formed products (compounds **19.5–19.7**) did not differ from that in the absence of halogens. The use of methylmagnesium iodide produced a small amount of ethyl 3-acetylazulene-1-carboxylate (compounds **19.4c** and **19.7c**) after the reaction of the reagent with the ester group. The unexpected presence of the Ph group in Position 5 (compound **19.10**) should be noted, even if the amount present was very small.



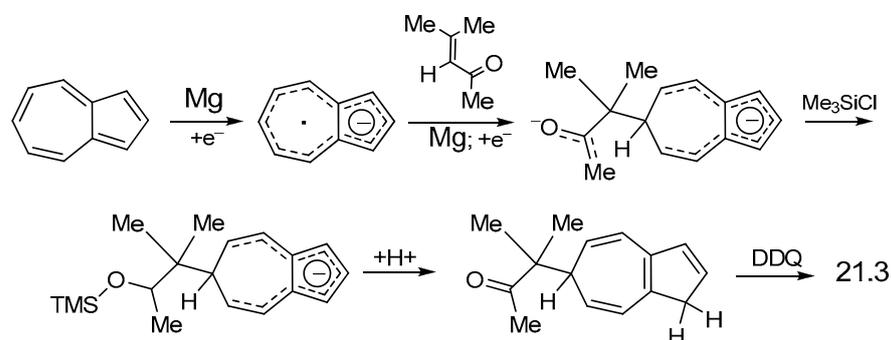
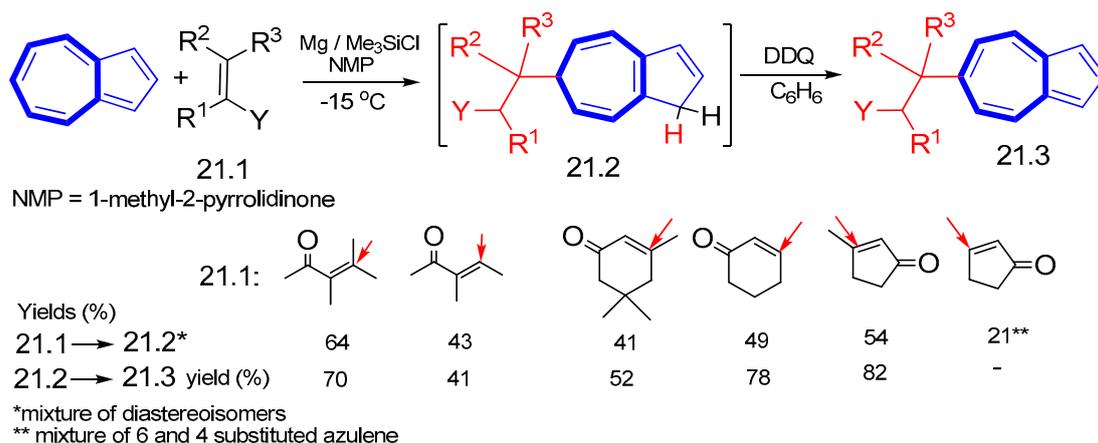
**Scheme 19.** Reaction of azulenes with organomagnesium compounds.

Grignard reagents have also been implicated in syntheses obtaining azulenic dimers, and the synthesis was reported by Hünig and Ort [36]. The reaction mixture contains, along with the dimers **20.2**–**20.4**, the intermediate, namely the addition compound **20.1**, in a rather large amount (Scheme 20). Both in this article and in that of Takase, it is assumed that the attack of the organomagnesium reagent produces in the first instance an anion radical.



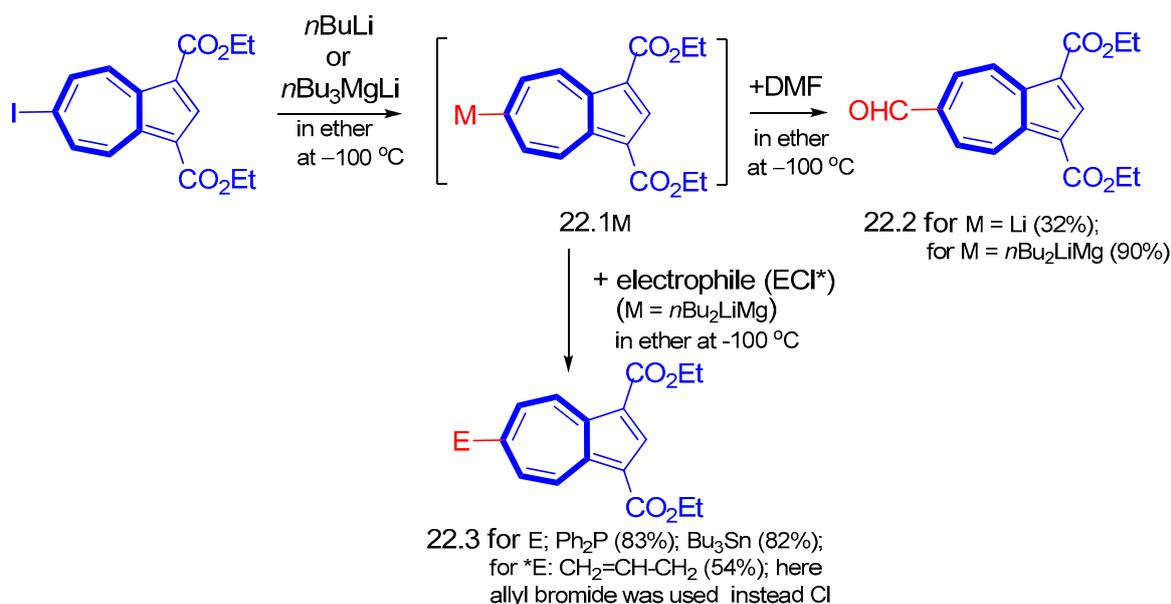
**Scheme 20.** Dimerization in the presence of a Grignard reagent.

The presence of an azulene anion radical was also postulated by Maekawa et al. in an article dealing with azulene coupling with  $\alpha,\beta$ -unsaturated ketones by Mg-promoted reduction [37]. As shown in Scheme 21, a reductive coupling of azulene with various  $\alpha,\beta$ -unsaturated ketones, **21.1**, takes place with magnesium in the presence of chlorotrimethylsilane in 1-methyl-2-pyrrolidinone. The electron transfers from the metal to azulene and affords the radical anion and then the dianion, and the involvement of  $\text{Me}_3\text{SiCl}$  generates the addition product **21.2**. The yields of this sequence were moderate, and those for the oxidation of **21.2** to **21.3** with DDQ were better. The authors' proposed mechanism for explaining the course of the reaction is shown in Scheme 21.



**Scheme 21.** Regioselective coupling of azulene at the double bond of  $\alpha,\beta$ -unsaturated ketones.

In order to achieve the halogen–metal exchange reaction with a metallic reagent for a new functionalization of azulene, 2- and 6-iodoazulene were used [38]. These compounds were reacted with *n*-butyllithium and lithium tri(*n*-butyl)magnesate (Scheme 22). The 6-azulenylmetal, reagent **22.1**, can act as the starting material for the synthesis of an important series of products. Thus, the reaction with electrophiles afforded the compound **22.3** and with DMF produced the aldehyde **22.2** used in several condensations.



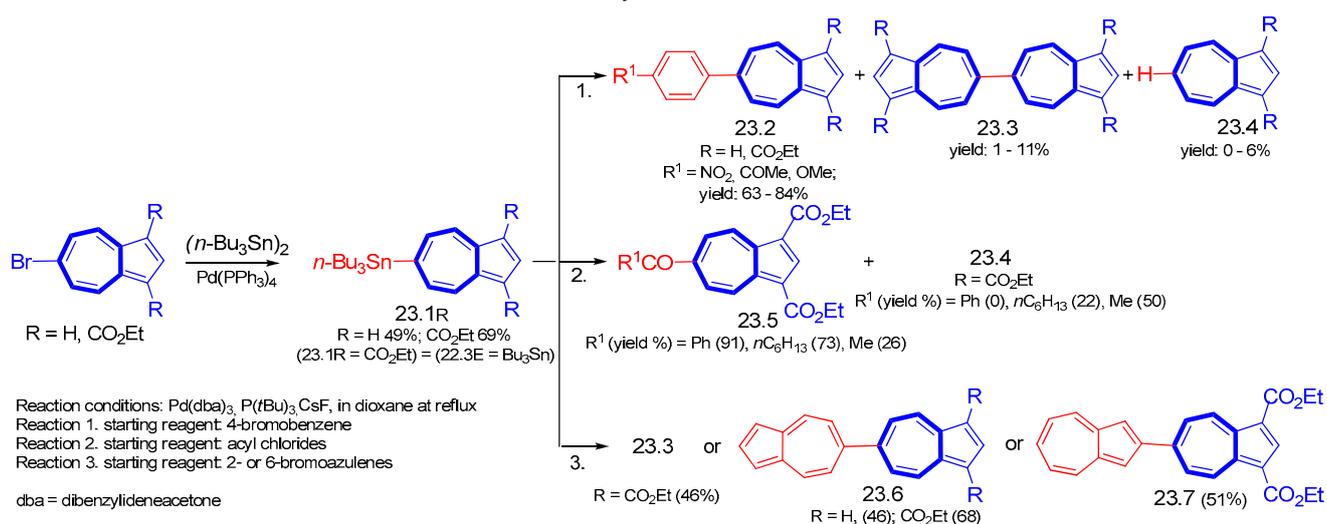
**Scheme 22.** Halogen–metal exchange reaction at Position 6 of azulene and subsequent replacement of metal.

## 6. Reactions Catalyzed by Transition Metal Complexes

The predominant way to obtain important azulene compounds substituted at the seven-atom ring is the cross-coupling reaction. This works under the catalytic influence of transition metal complexes. Therefore, the present subchapter will develop this topic with predilection, leaving the few examples that do not belong to this class of reactions to be mentioned at the end of the subchapter.

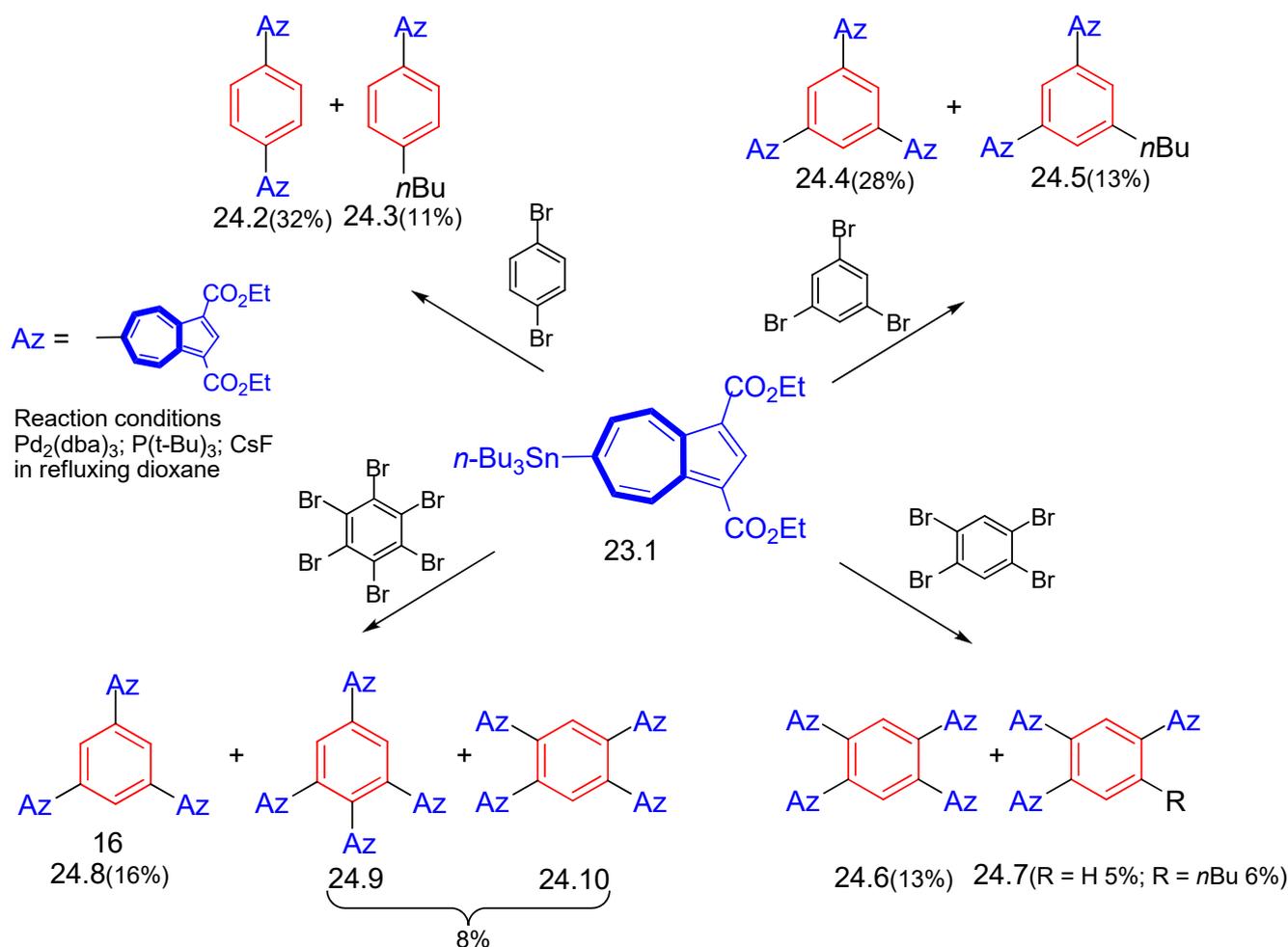
### 6.1. Stille Cross-Coupling

The Stille cross-coupling syntheses at the seven ring, described by Ito et al. [39], start from organotin derivatives: **23.1R**. As described in Scheme 23, this organometallic compound results from the substitution of halogen in Position 6 with 1,1,1,2,2,2-hexabutyldistannane, (*n*-Bu<sub>3</sub>Sn)<sub>2</sub>, catalyzed by Pd(0) [40]. This reaction occurs in moderate to good yields (for compound **23.1R** = CO<sub>2</sub>Et (69%) ≡ **22.3E** = *n*Bu<sub>3</sub>Sn (82%) Scheme 22). Several classes of halogenoderivatives were reacted with azulenylnit compounds **23.1** in the presence of Pd(dba)<sub>3</sub>.P(*t*Bu)<sub>3</sub>.CsF. Starting from 4-substituted chlorobenzenes (Entry 1), the reaction mixture contained, together with a majority of 6-phenylazulenes, **23.2**, small amounts of the dimer **23.3** and the product of metal elimination, **23.4**. The acyl chlorides (Entry 2) produced the substituted product **23.5** and, depending on the acyl nature, the elimination compound **23.4**. When halogenoazulenes were used (Entry 3) the dimers **23.3**, **23.6**, or **23.7** were formed in moderate yields.



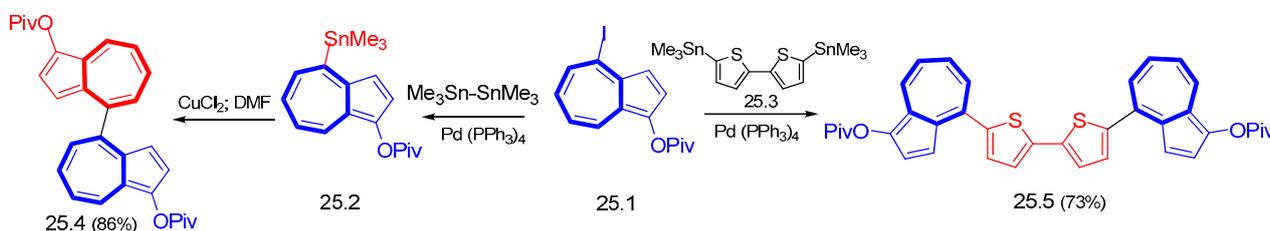
**Scheme 23.** Stille reaction at azulene Position 6.

Another target proposed by Ito et al. [41] was to obtain substituted benzene with multiple azulene-6-yl moieties (Scheme 24) starting from benzene with bromine atoms in different positions. The reaction afforded compounds substituted only with azulenyl groups, **24.2**, **24.4**, and **24.6**, the benzene with these groups, and one *n*Bu group, **24.3**, **24.5**, and **24.7**, as a result of the transfer of one *n*Bu from the organotin reagent. The attempt to substitute all six positions in benzene failed and the products obtained contained positions occupied by azulenyl but also positions where bromine had been eliminated. All the experiments described in Scheme 24 occurred with modest yields.



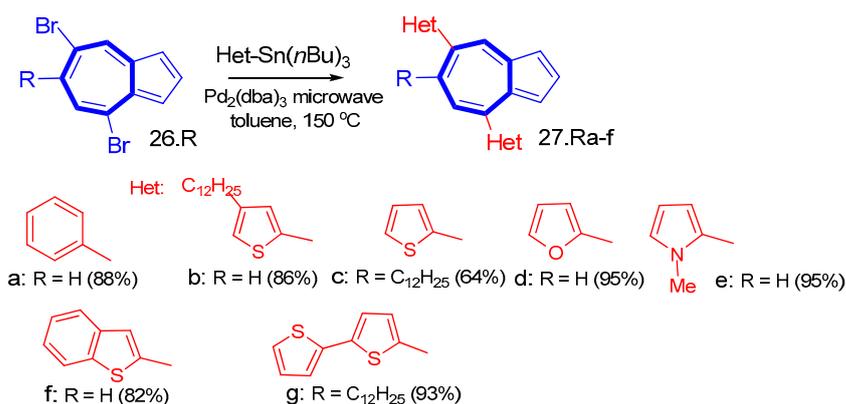
**Scheme 24.** Stille reaction of benzene with bromine atoms in different positions.

Stille condensation was also used by Crombie et al. for building substituted azulenes and oligoazulenes [42]. In their works, the starting reagents were both azulene with the  $\text{SnMe}_3$  group, **25.2**, and other compounds possessing this substituent, **25.3** (Scheme 25). It should be noted the surprising reaction of the compound **25.2** with the formation of the dimer **25.4** occurred with an excellent yield.



**Scheme 25.** Stille reaction with organotin compounds.

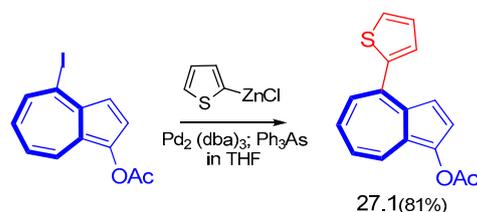
The research works of Amir et al. are oriented in the same direction, using  $\text{Pd}_2(\text{dba})_3$  as catalyst. They condensed the halogenoazulene **26.1** with various trimethylstannyl derivatives in the presence of microwaves, with the aim of realizing the azulene-based conjugated oligomers **27Ra–f** (Scheme 26) [43,44]. As can be seen, the authors started from a wide range of heterocyclic compounds and the reaction yields were very good.



**Scheme 26.** Condensation of halogenozulene with various trimethylstannyl derivatives.

### 6.2. Heck–Negishi Condensation

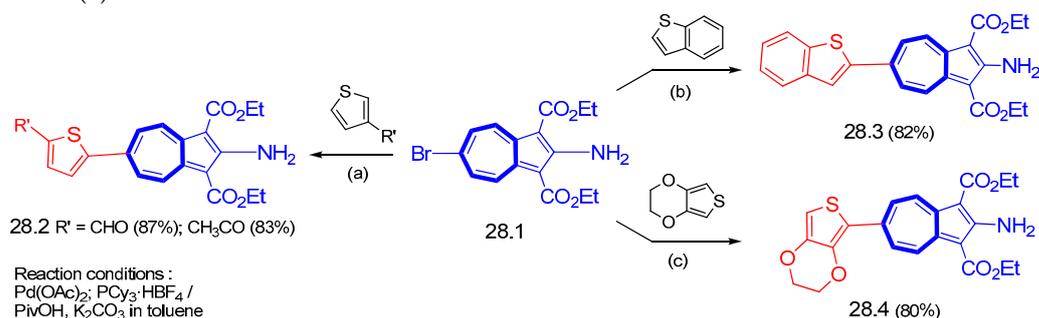
This procedure represents an alternative to the Stille reaction. Here, Sn was replaced by Zn in the organometallic reagent, which is coupled with halogenozulene in the presence of the Pd catalyst, and the product **27.1** (Scheme 27) resulted in a good yield [42].



**Scheme 27.** Heck–Negishi condensation.

### 6.3. Syntheses of Other Thienylazulene Derivatives

Scheme 28 shows a route for obtaining 6-thienylazulene derivatives [45] which, with respect to their stable redox properties, may be expected to provide good-performance organic electronics. In addition to the substitute thiophene, route (a) in Scheme 28, Shoji et al. used benzo[b]thiophene and 2,3-dihydrothieno [3,4-b][1,4]dioxine as partners in the cross-coupling with the 6-bromide **28.1**, with Position 2 occupied, for the generation of the products **28.3** and **28.4** via Routes (b) and (c) along the compounds **28.2** resulted on the Route (a).



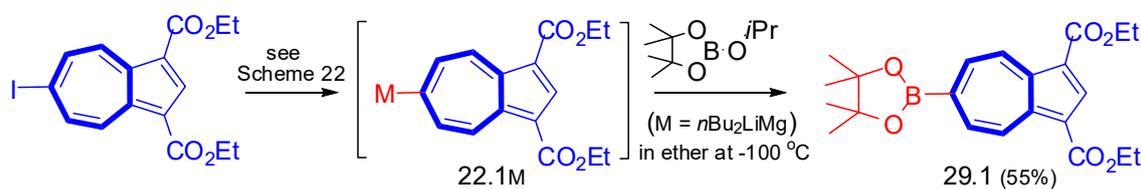
**Scheme 28.** Palladium catalyzed reaction between the 6-bromoazulene **28.1** and thiophene derivatives.

### 6.4. Suzuki–Miyaura Cross-Condensation

One of the particularly successful procedures by which the seven-membered ring can be substituted is the Suzuki–Miyaura cross-condensation. Together with halogenoderivatives, boronate reagents represent the components for this transition-metal catalyzed cross-coupling reaction. The halogen and the boryl group may belong to azulene or the other reagent that participates in the condensation.

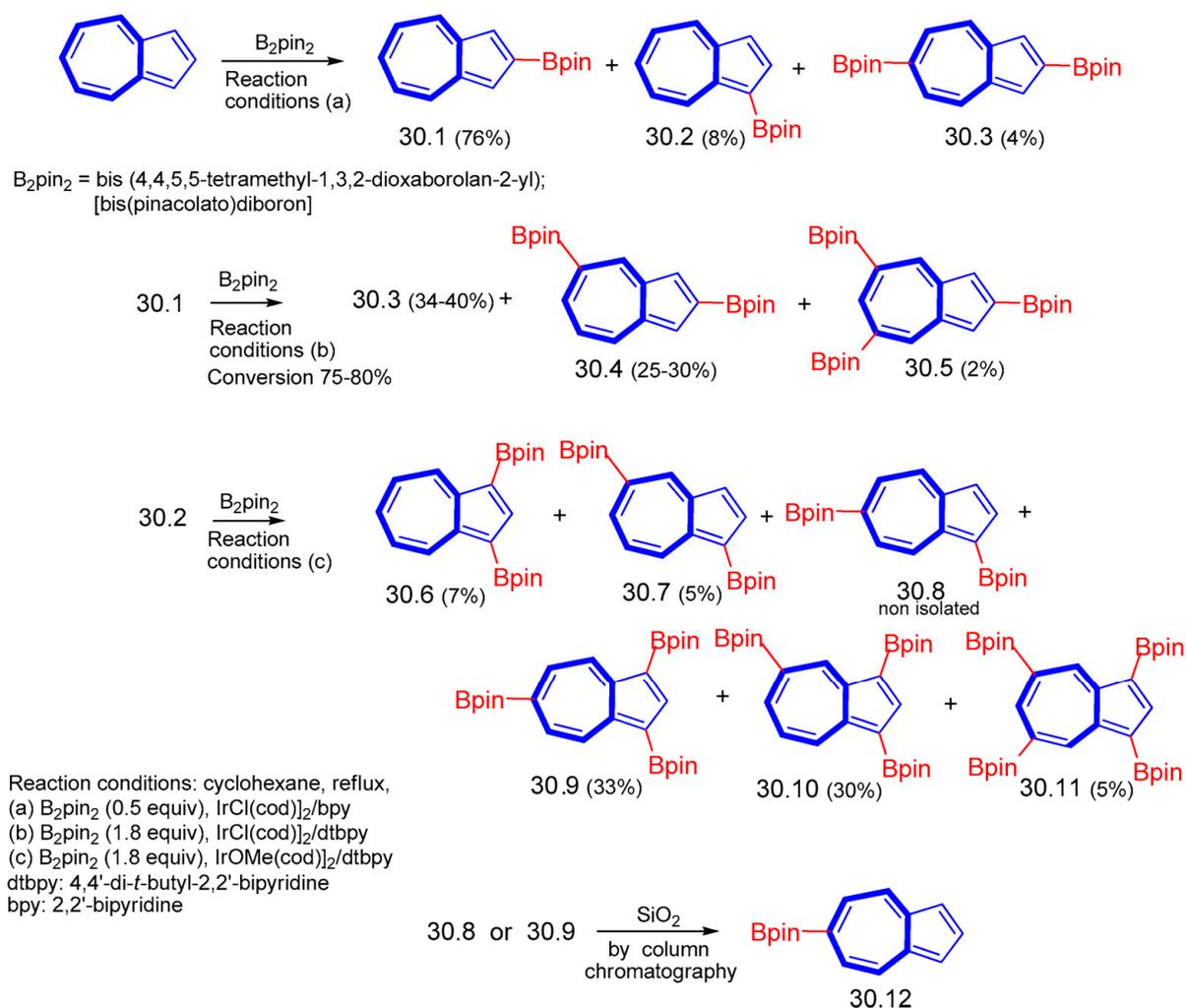
Several pieces of information on the methodology to borylate the seven-membered ring of azulenes will be briefly mentioned below. Thus, Scheme 29 completes Scheme 22

by introducing the replacement of the metal substituent with a boryl group [38]. The reaction with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane furnished the desired boronate **29.1**.



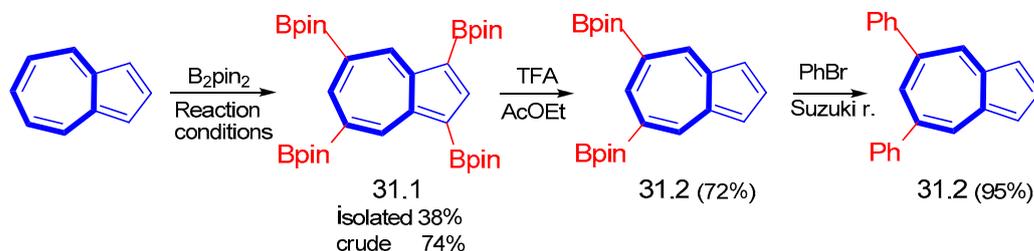
**Scheme 29.** Borylation of azulenes.

In the syntheses included in Scheme 30, the C-H bond is activated by the catalytic presence of the iridium compound and azulene, as well as borylated azulenes being used as starting materials [46]. In the absence of a substituent, the borylation at the seven-membered ring occurs with only a 4% (compound **30.3**) yield; however, when Bpin is present at five-membered ring (compounds **30.1** or **30.2**), the substitution at the seven-atom ring increases significantly. It should be noted that Positions 5 and 6 of azulene are preferentially occupied. The authors explain how electronic and steric effects influence the ratio of products in the reaction mixture. The article also reports the deborylation of compounds **30.8** and **30.9** to **30.12** by chromatography on an  $\text{SiO}_2$  column.



**Scheme 30.** Borylation at the azulene seven-membered ring.

Somewhat more recently, the polyborylation of azulene was also carried out, albeit with a modest yield [47]. The formed compound **31.1** was then treated with TFA in AcOEt and the deborylated compound **31.2** was subsequently Suzuki-reacted to 5,7-diphenylazulene, **31.3** (Scheme 31). The last two reactions occurred with good yields.

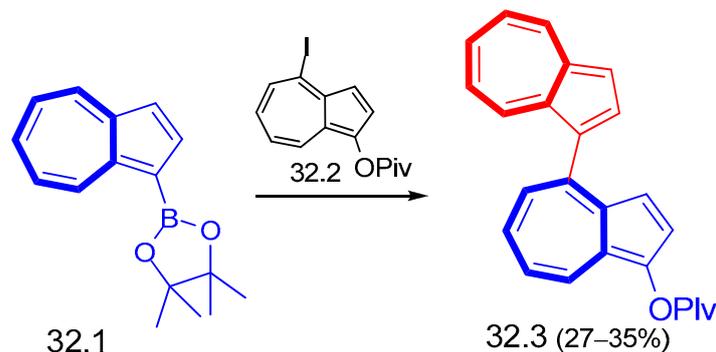


Reaction conditions:

[IrOMe(cod)]<sub>2</sub> (20%), 4,4'-dmbpy (40%), THF, 85 °C, B<sub>2</sub>pin<sub>2</sub> (4.4 equiv); *t*BuOK  
 4,4'-dmbpy = 4,4'-dimethyl-2,2'-bipyridyl.

**Scheme 31.** Polyborylation and deborylation at the azulene seven-membered ring; Suzuki coupling.

From the multitude of Suzuki cross-condensations that have been described in the literature, only a few significant examples have been chosen and will be developed below. At the beginning, certain examples of azulene dimerizations and oligomerizations will be given using the Suzuki coupling. Thus, the complex of Pd(OAc)<sub>2</sub> catalyzes the reaction between the borylated azulene **32.1** and the halogenoazulene **32.2** [47], giving the dimer **32.3** with a moderate yield (Scheme 32).



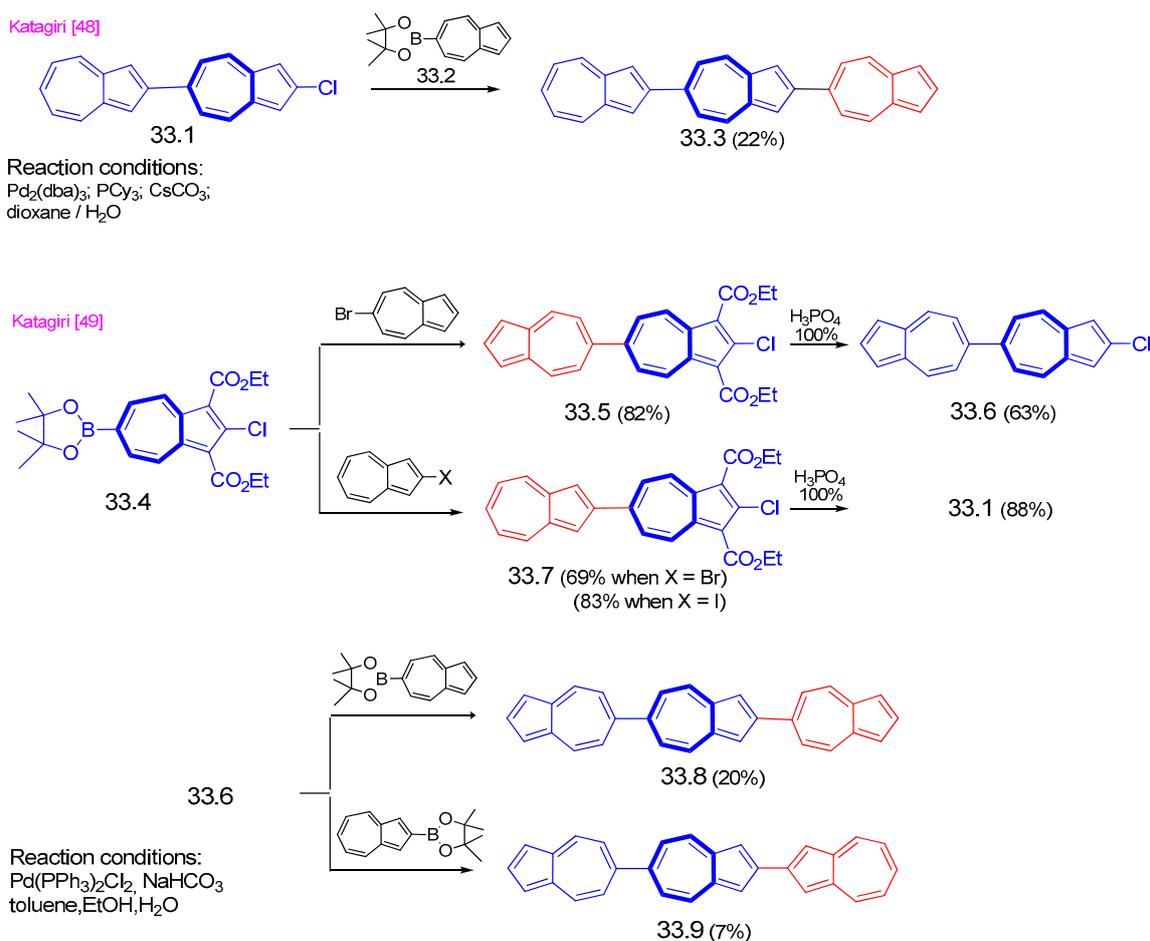
Reaction conditions:

Pd(OAc)<sub>2</sub>; (*o*-biphenyl)PCy<sub>2</sub>; Ba(OH)<sub>2</sub>;  
 dioxane / H<sub>2</sub>O

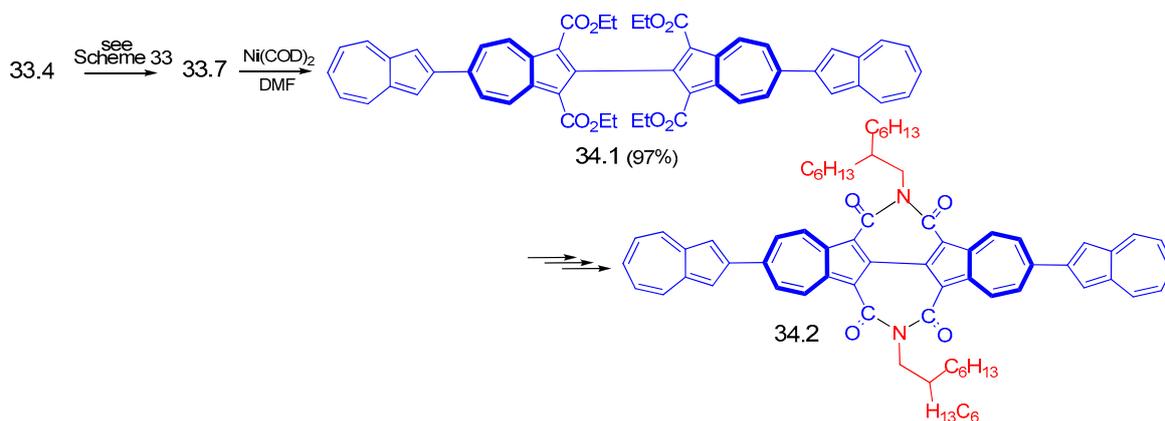
**Scheme 32.** Azulene dimerization by Suzuki condensation.

Linear expanded azulene  $\pi$ -conjugated oligomers can play a part in the building of OFET materials; thus, Katagiri et al. [48,49] developed the syntheses of such compounds. The first attempt started from the halogenated dimer **33.1** and the boryl ester **33.2** without other substituents, and the reaction yield was modest (Scheme 33). Since nucleophilic agents, for electronic reasons, can more easily attack Position 6 in azulenes substituted in Positions 1 and 3 with CO<sub>2</sub>R groups, compounds with this structure **33.4** have been used in many boronyl group substitutions with good results. Due to the tendency of Position 2 to be attacked by a nucleophile, one starts from azulenes substituted in this position.

Showing similar concerns, Gao X. et al. [50] have obtained 2,2''-biazulene-1,1',3,3'-tetracarboxylic diimides, **34.2**, with photophysical properties as promising organic electronic materials (Scheme 34). The synthesis starts from the sequence **33.4**–**33.7** described in Scheme 33.

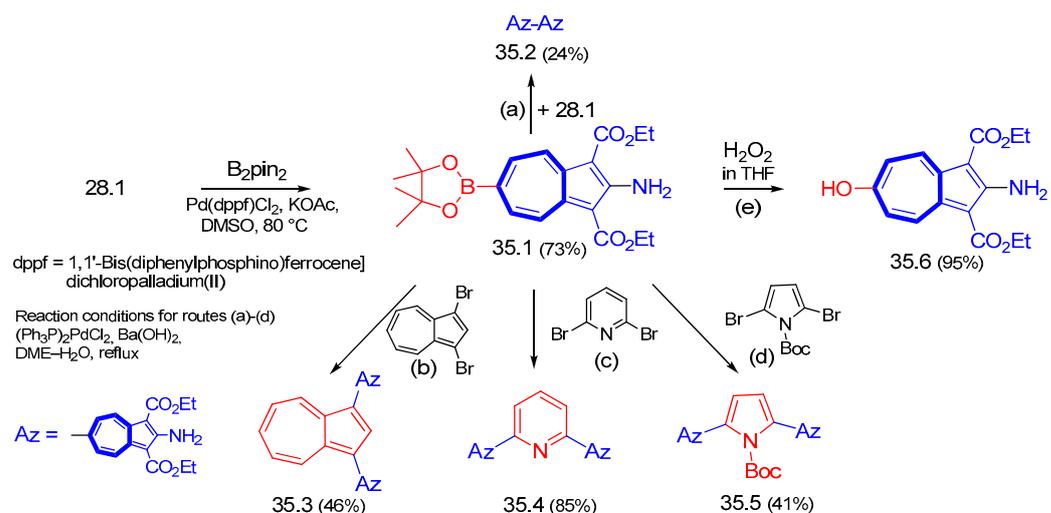


Scheme 33. Azulene oligomerization by Suzuki condensation.



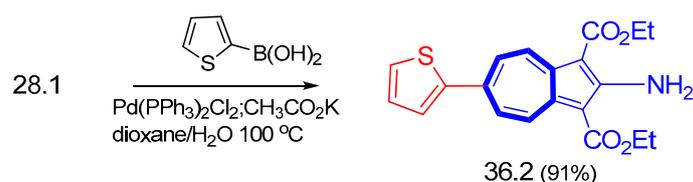
Scheme 34. Gao X. synthesis of cyclic diimide.

The raw material **35.1** used in Scheme **35** was prepared by replacing the halogen in Position 6 in the compound **28.1** with the boronyl group, and several interesting products were obtained using the boronate **35.1** [51]. In addition to the azulene dimer and trimer **35.2** and **35.3**, the heterocyclic compounds **35.4** and **35.5** were also prepared (Routes a, b, and c, d). It should be noted that Murfin et al. replaced the boronyl group in **35.1** with a hydroxyl as in compound **35.6** (Route e), which may have further applications in two-photon fluorescence imaging [52].



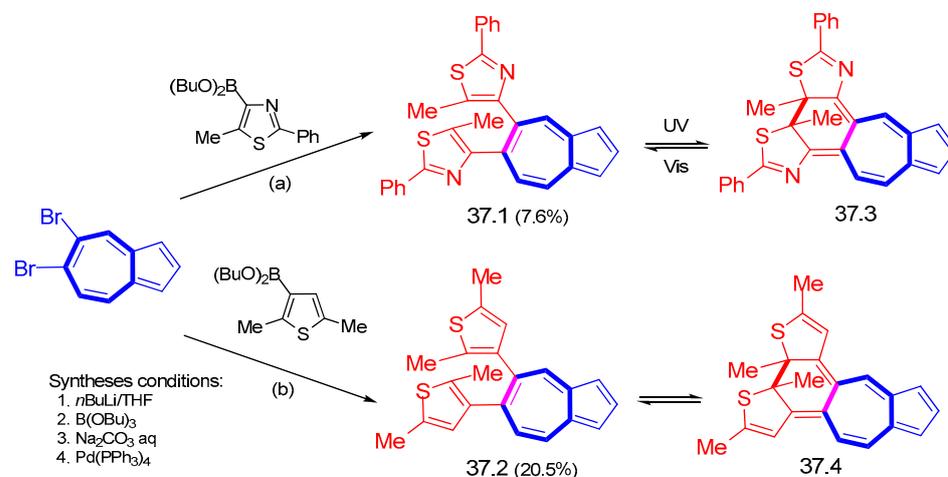
**Scheme 35.** Suzuki cross-coupling syntheses.

In the examples developed above, a boronyl group is attached to azulene, whereas the following Suzuki syntheses use other borylated compounds that are coupled with halogenoazulenes. Thus, Scheme 36 illustrates the use of boronated thiophene with the 6-bromoazulene **28.1** [53].



**Scheme 36.** Suzuki reaction with thiophen-2-ylboronic acid.

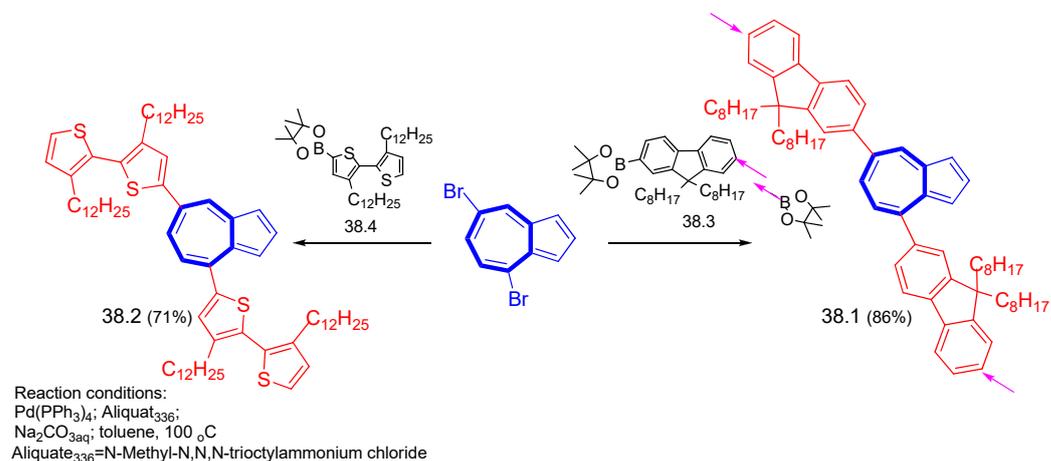
In a study regarding photochromism, the “diarylethene” derivatives **37.1** and **37.2**, incorporating a double bond of the seven-atom ring as the “ethene” moiety, were synthesized by Suzuki coupling between five-membered heteroaryl boronates and 5,6-dibromoazulene as shown in Scheme 37 [54]. The derivative **37.1** with thiazole groups showed photochromism, while the compound **37.2** with thiophene rings did not show any photochromism.



**Scheme 37.** Obtainment of “diarylethenes” 1 and 2 and their photochromic behavior.

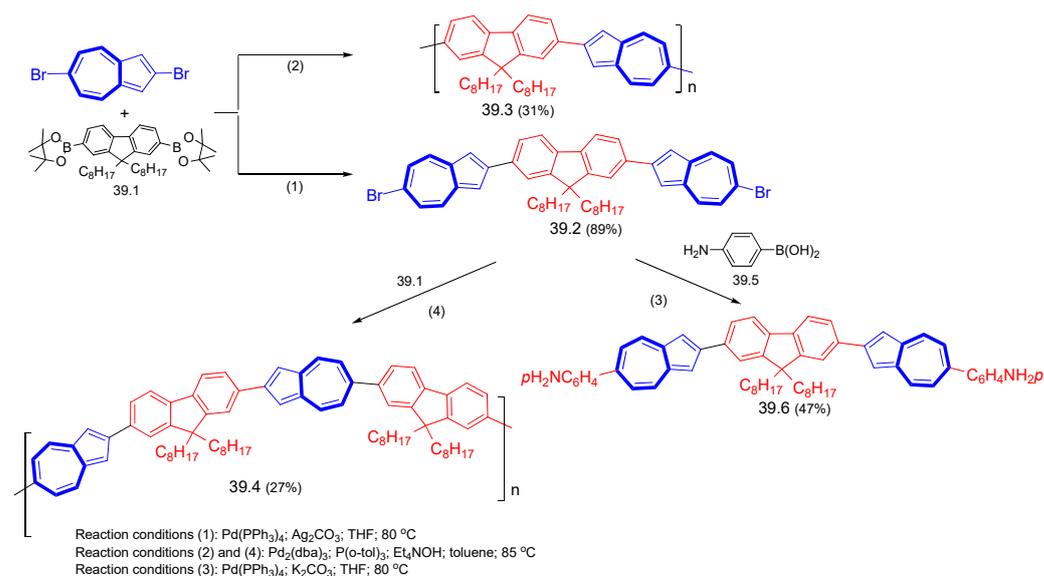
The Suzuki–Miyaura protocol was also used for the synthesis of certain polymers. During the study of the optoelectronic and stimuli-responsive properties of several materials, Murai et al. [55] proved that 4,7-bis(9,9-dioctylfluoren-2-yl)azulene, **38.1**, and

4,7-bis(3,3'-didodecyl-2,2'-bithienyl)azulene, **38.2**, exhibit stimuli-responsive behavior in the solid state with spin-coated thin films undergoing rapid and reversible color switching. Therefore, they synthesized these compounds via the Suzuki–Miyaura route as shown in Scheme 38. Next, they treated the reagent **38.3**, in which the position indicated by the arrow is also boronated, with a mixture of 1,3 and 4,7-dibromoazulenes, and the properties of the resulting polymer were studied.



**Scheme 38.** Synthesis of bithienyl-azulene, **38.1**.

The target of studies undertaken by Gao X. et al. was to find compounds that can improve proton responsiveness and electrical conductivity [56,57]. Until their research, most compounds with these characteristics included azulenes substituted in Positions 1 and 6. In their work, Gao X. et al. paid attention to systems with 1,3-free-2,6-connected azulene units in the molecule or polymeric backbone. The generation of oligomers (**39.2** and **39.6**) and polymers (**39.3** and **39.4**) belonging to these compound classes followed the Suzuki–Miyaura protocol as can be seen in Scheme 39. The coupled reagents were 1,6-dibromoazulene and 2,2'-(9,9-dioctyl-9H-fluorene-2,7-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **39.1**.

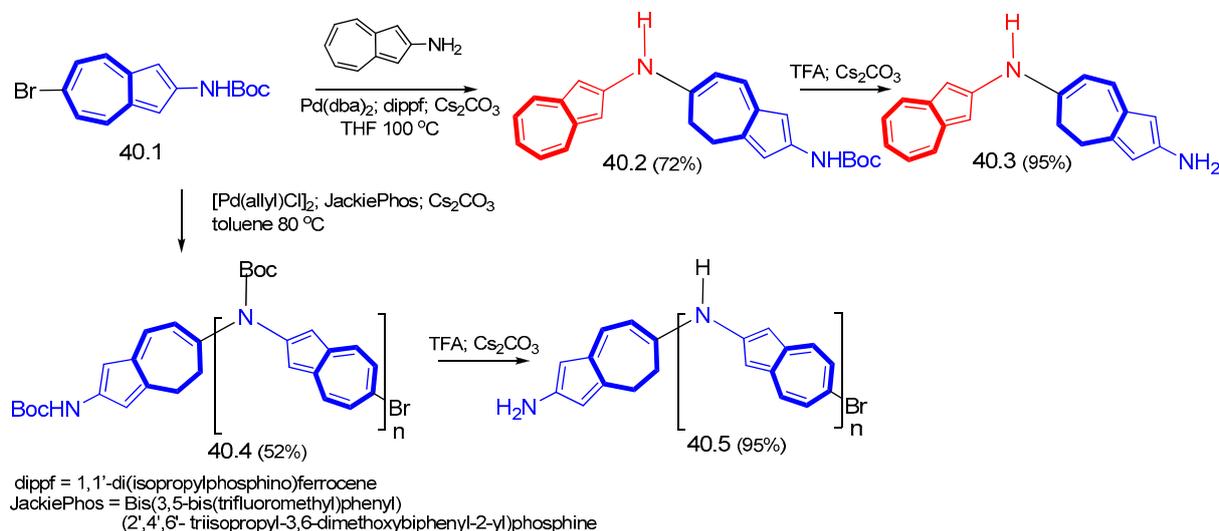


**Scheme 39.** Oligomers and polymers by Suzuki–Miyaura cross-coupling.

In 2020, a comprehensive and interesting review was published on “azulene-based molecules, polymers, and frameworks” [58]. The authors mainly refer to compounds with optoelectronic and energy applications.

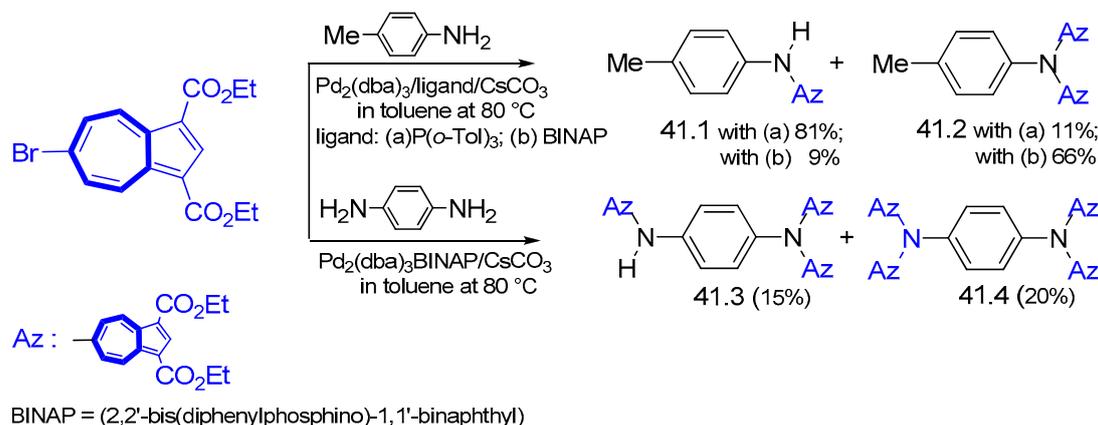
### 6.5. Various Syntheses Catalyzed by Transition Metal Complexes

The valuable photophysical properties and proton conductivity of poly [2(6)-aminoazulene], **40.5**, have boosted the study of these compounds, as well as studies of dimeric aminoazulene, **40.3** [59]. In order to produce these compounds, the Buchwald–Hartwig procedure shown in Scheme 40 was used.



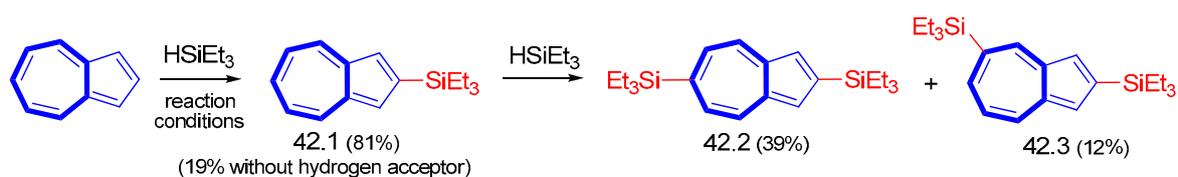
**Scheme 40.** Buchwald–Hartwig procedure for obtaining dimeric aminoazulenes and poly [2(6)-aminoazulene].

Other aminoazulenes, **41.1–41.4**, with interesting chemical properties have been reported by Ito et al. [60]. These compounds were obtained from the reaction of *p*-toluidine and *p*-phenylenediamine with 6-bromoazulene as shown in Scheme 41, and the ratio between the formed derivatives depended on the used ligand.



**Scheme 41.** Palladium-catalyzed reaction of phenylamines with 6-bromoazulene.

The reaction of dehydrogenative silylation (Scheme 42) is catalyzed by an iridium complex (Scheme 40) and takes place in two stages, both based on the chemo- and regioselective activation of  $\text{C}_{\text{sp}^2}\text{-H}$  bonds at five-atom and seven-atom azulene rings [61]. The first step occurs with excellent yields and provides 2-silylazulene, **42.1**, even without any directing groups. However, without the presence of a hydrogen acceptor, the yield drops to 19%. The second-ring silylation does not have the same efficiency and leads to a mixture of isomers, **42.2** and **42.3**.



Reaction conditions: catalyst:  $[\text{Ir}(\text{OMe})(\text{cod})_2]_2$ ; ligand: 3,4,7,8-tetramethyl-1,10-phenanthroline; hydrogen acceptor: 3,3-Dimethyl-1-butene in cyclohexan

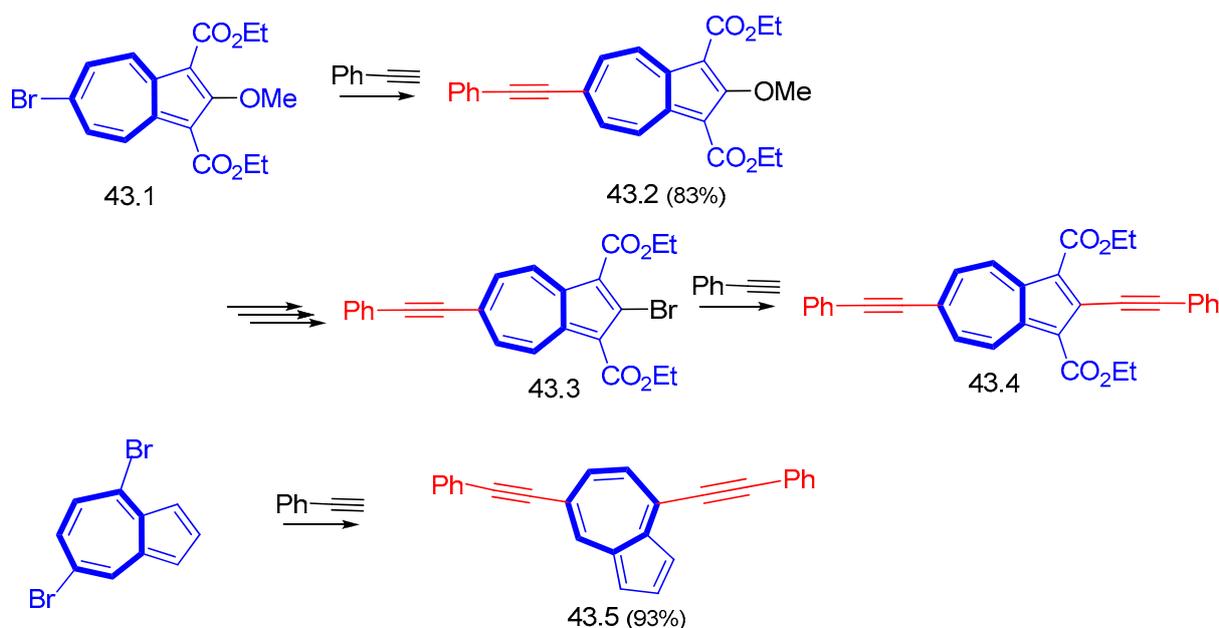
**Scheme 42.** Dehydrogenative silylation of azulene.

## 7. Azulene Derivatives Containing Ethynyl Group(s)

A frequented field of azulene chemistry is represented by the compounds that contain the ethynyl group in the molecule. In addition to their interesting physicochemical properties, the compounds of this class can play the role of electrochromic materials or materials for the construction of high-performance semiconducting polymers for transistors and solar cells. This is why certain examples from this broad class of compounds will be briefly presented below.

### 7.1. Azulenes Substituted with Ethynyl Groups

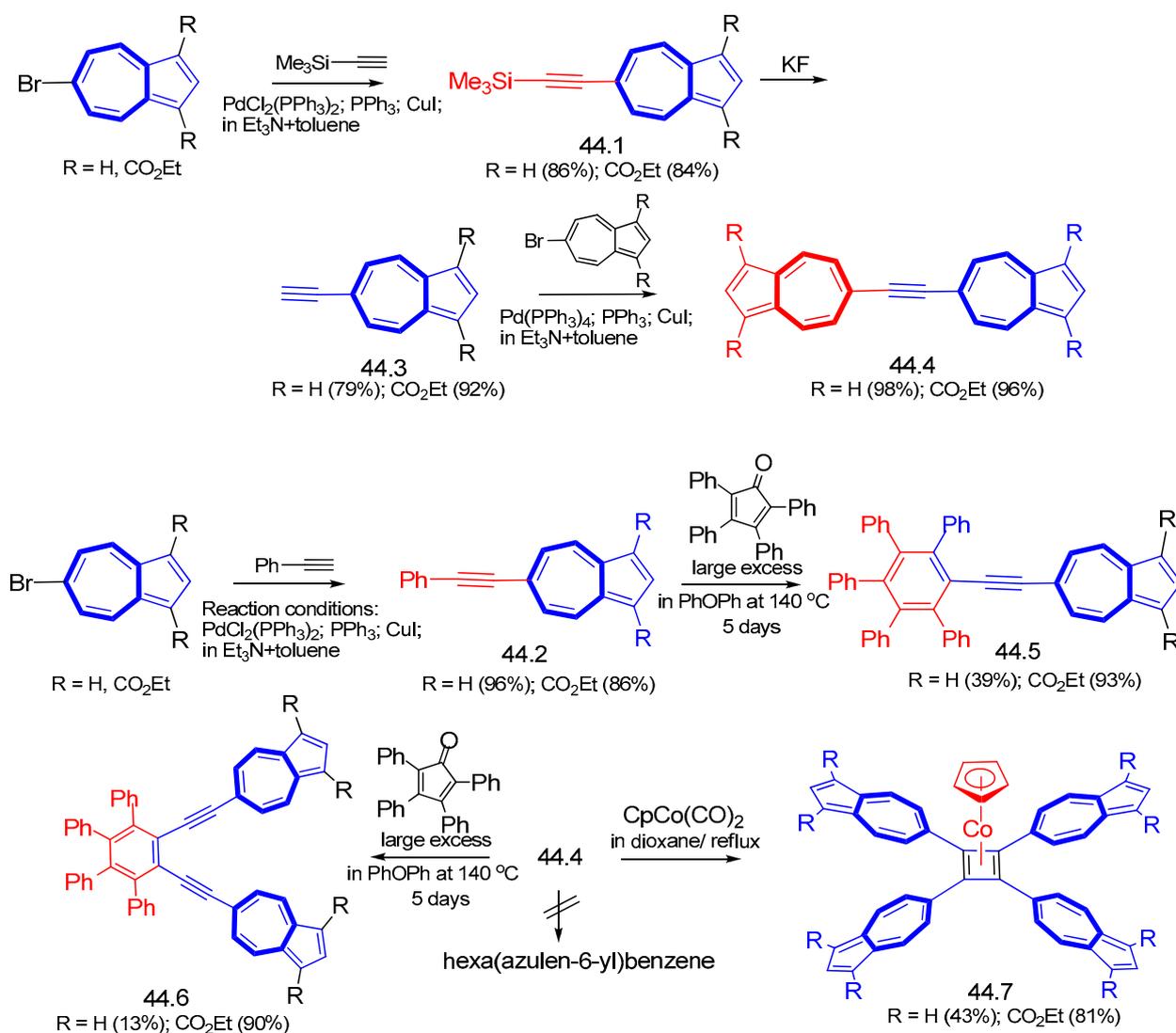
During their research of the properties of azulenes substituted with ethynyl groups, Koch et al. found that a 2,6-connection in azulene, as seen in compound **43.4**, “exhibits quite interesting and unique optical and physical properties in comparison with the other isomers of di(phenylethynyl)azulenes” [62]. Therefore, they developed a route for the synthesis of such products, described in Scheme 43. As starting materials, halogenated azulenes were used. It should be mentioned that as the activating group in the azulene Position 2, OMe was used here instead of the amino group from compound **28.1**, and the reaction with ethynylbenzene was catalyzed by the Pd complex and occurred with good yields. The subsequent reactions at the OMe group afforded bromoazulene, **43.3**, which was transformed into 2,6-di(phenylethynyl)azulene, **43.4**. The reaction of 4,7-dibromoazulene and ethynylbenzene gave the corresponding disubstituted product **43.5**.



Reaction conditions:  
 $\text{PdCl}_2(\text{PPh}_3)_2$ ;  $\text{PPh}_3$ ;  $\text{CuI}$ ;  
 in  $\text{Et}_3\text{N}$ +toluene

**Scheme 43.** Reaction of bromoazulenes with ethynylbenzene.

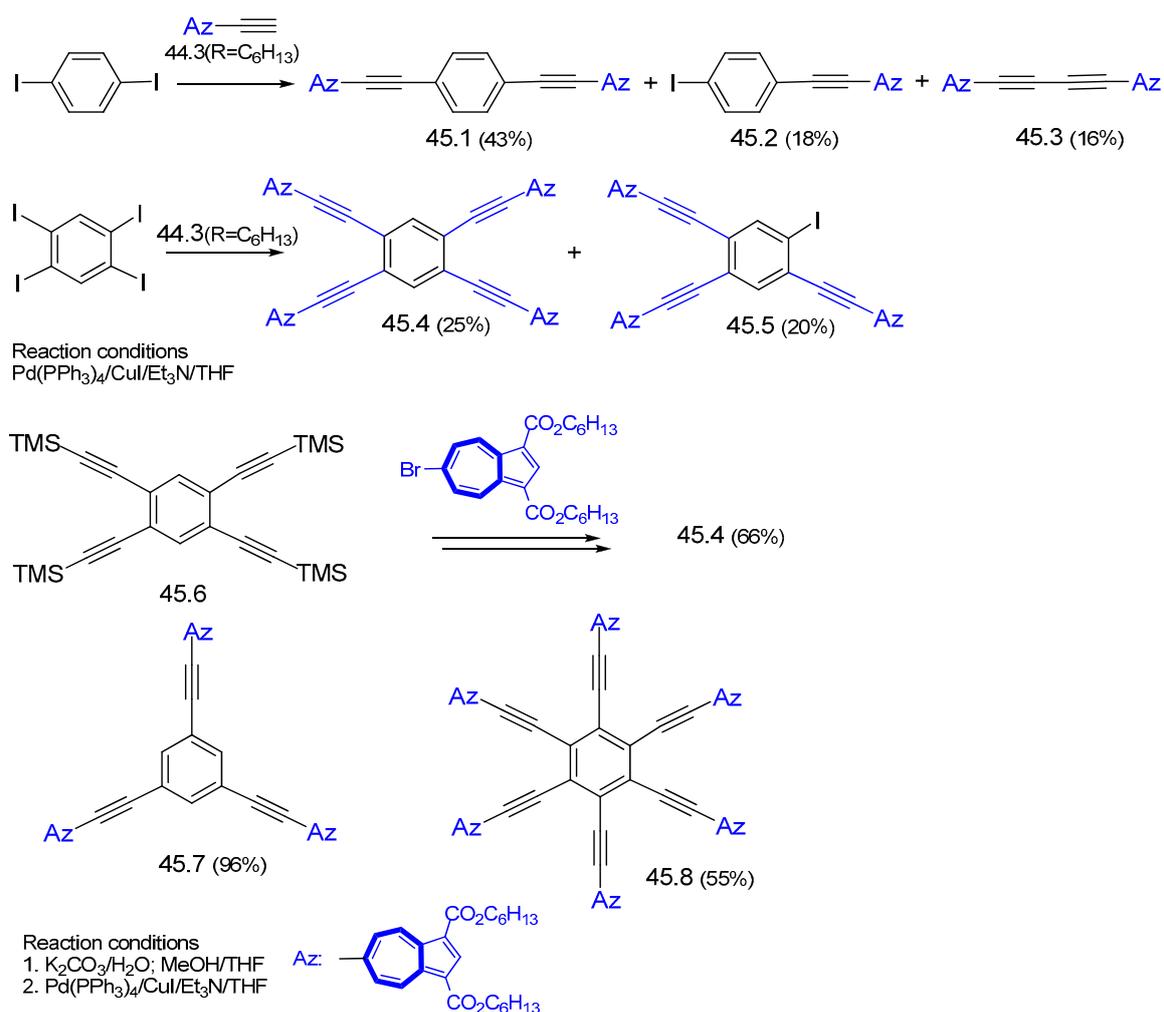
A number of papers elaborated by Ito et al. have dealt with the obtainment, properties, and possible technical use of ethynylazulenes. Following the Sonogashira–Hagihara conditions, they reacted 6-bromoazulene with ethynyltrimethylsilane and with ethynylbenzene in the catalytic presence of the palladium complex as shown in Scheme 44 [63,64]. Two observations should be made in relation to this reaction. The halogen in Position 6 is not activated by effective substituents in Position 2 as in the case of the compounds **28.1** or **43.1** without a decrease in yield. In addition, the presence of CO<sub>2</sub>Et groups in Positions 1 and 3 does not improve the results of the reactions. The resultant first products **44.1** and **44.2** were then used as a starting material for subsequent reactions. Thus, the Me<sub>3</sub>Si group was removed from the compound **44.1** to yield the ethynylazulene **44.3**, which afforded the dimer **44.4** after reaction with the starting bromoazulene. Both the phenylethynylazulenes **44.2** and the dimer **44.4** were involved in the Diels–Alder reaction with a large excess of tetraphenylcyclopentadienone and the polysubstituted benzene **44.5** and **44.6** were obtained. The desired target, namely the generation of hexa(6-azulenyl)benzene, failed. The reaction of the dimer **44.4** under the influence of CpCo(CO)<sub>2</sub> led to the formation of the cobalt complex **44.7**.



**Scheme 44.** Reaction sequences starting from 6-bromoazulene, **44.1**, and ethynyltrimethylsilane or ethynylbenzene.

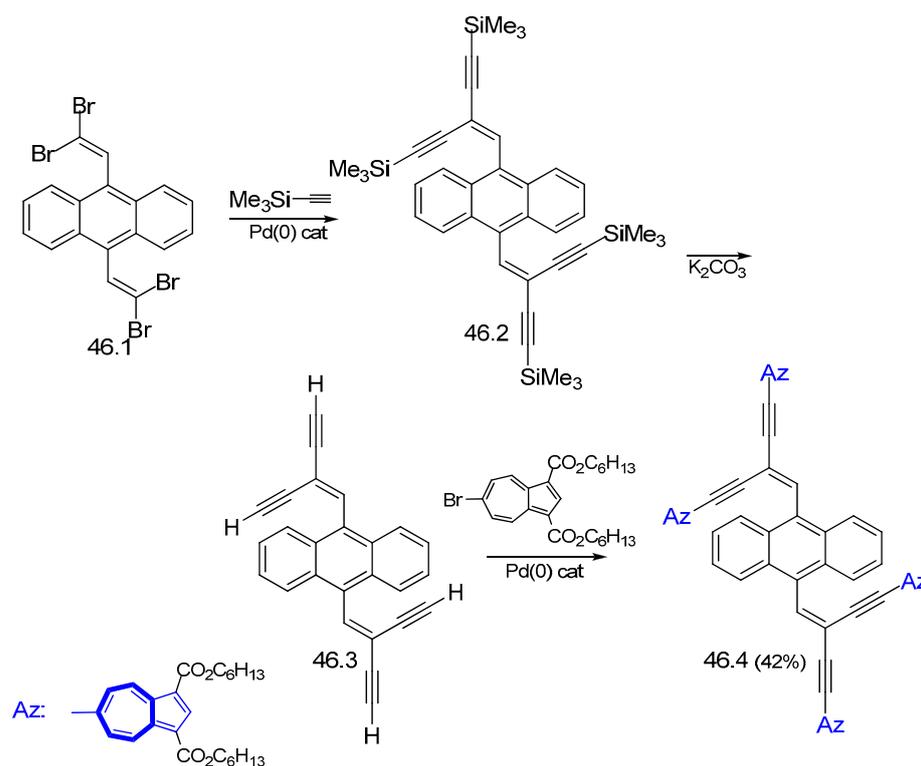
As a result of the synthesis failure of hexa(6-azulenyl)benzene, Ito et al. have focused their attention on obtaining the corresponding hexa(6-azulenylethynyl) derivative [65]. At

the same time, a series of poly(6-azulenylethynyl)benzene derivatives were described in this study (Scheme 45) because these systems can take part in the building of advanced materials for electrochromic application with liquid crystalline behavior. Sonogashira–Hagihara conditions were applied to the halogenated compounds of benzene or azulene. Depending on the structure of the benzene iodides after the reaction with ethynylazulene, a mixture of compounds, 45.1–3, 45.4, and 45.5, was formed. The reaction of bromoazulene with ethynylbenzenes occurred with better results. The reaction of TMS elimination from 45.6 and the subsequent condensation of formed bromoazulene were developed without the separation of ethynyl compounds. In this way, compounds 45.4 and 45.7 were obtained with good yields, but especially the interesting compound 45.8 with all benzene positions substituted by azulenylethynyl groups.



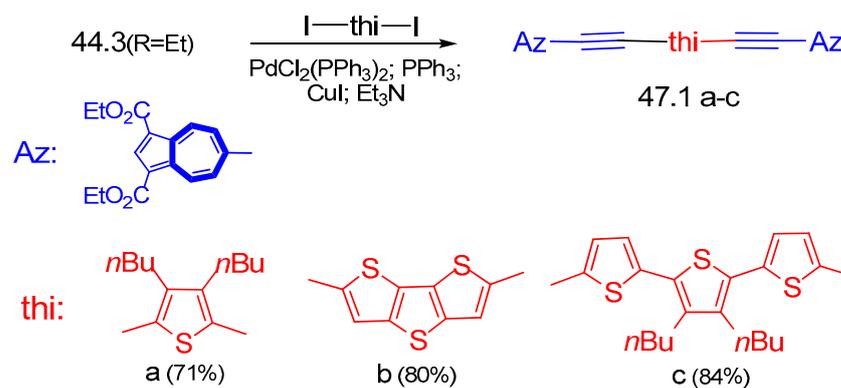
**Scheme 45.** Sonogashira–Hagihara reaction for the generation of azulenylethynylbenzenes.

Continuing the interest in the realization of electrochromic materials with a strong absorption in the near-infrared region, Ito et al. synthesized the compound 46.4 [66]. This 9,10-anthracenediyl spacer with azulene-substituted enediyne groups in Positions 9 and 10 was obtained as described in Scheme 46, and the product properties were investigated by the authors. The polyethynyl compound 46.3, obtained as in Scheme 46, was treated with 6-bromoazulene in the presence of a Pd(0) catalyst and afforded the attempted product 46.4.



**Scheme 46.** Synthesis of 9,10-anthracenediyl with azulene-substituted enediyne groups at Positions 9 and 10.

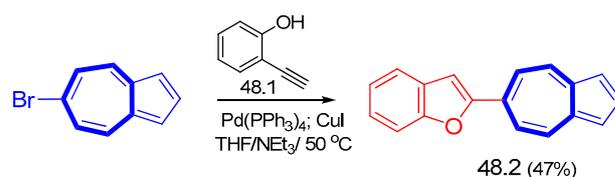
Sonogashira–Hagihara reactions have continued to attract the attention of researchers. Thus, Okujima et al. obtained bis-substituted azulenylethynyl thiophenes, terthiophenes, and dithienothiophenes following the procedure described in Scheme 47 [67]. The properties of the products are expected to provide high-performance photovoltaic cells.



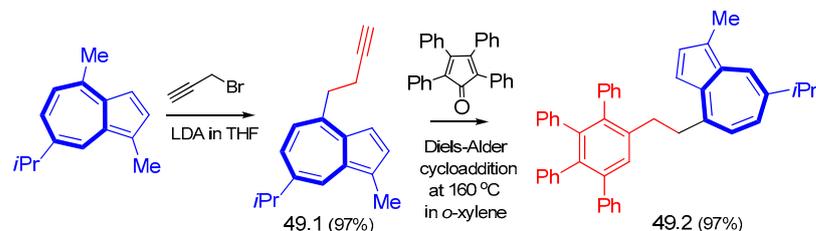
**Scheme 47.** Sonogashira–Hagihara reaction based on reagents with thiophene in the molecule.

The synthesis of 6-(2-benzofuryl)azulenes, **48.2**, with marked halochromic and fluorescent behaviors was accomplished by Shoji et al. by Sonogashira coupling of the haloazulene with 2-ethynylphenol, **48.1**, followed by an intramolecular cyclization reaction (Scheme 48) [68].

An interesting reaction in which an azulenic compound **49.1** with an ethynyl group in the molecule is involved in a Diels–Alder cycloaddition to build a benzene ring, as in the product **49.2** shown in Scheme 49 [69]. The generation of starting **49.1**, as well as its cycloaddition, occurred with excellent yields.



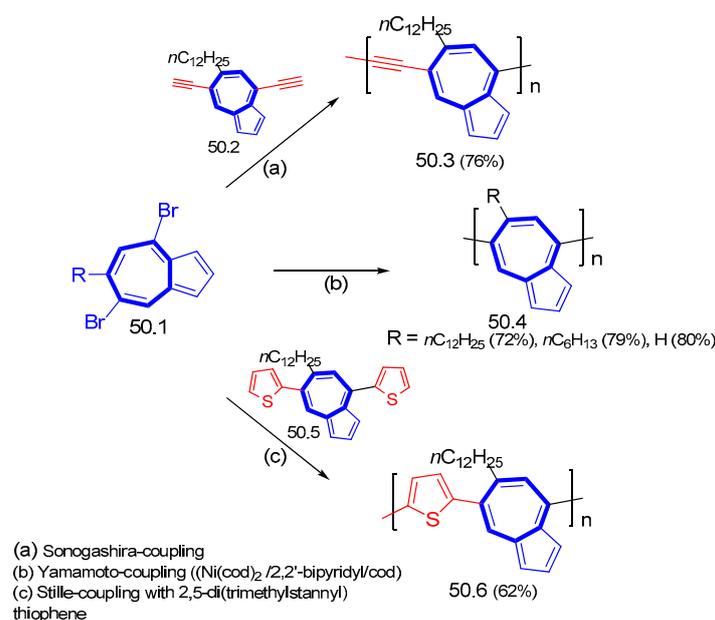
**Scheme 48.** Sonogashira coupling of the haloazulene with 2-ethynylphenol.



**Scheme 49.** Diels–Alder cycloaddition to build the product 49.2.

### 7.2. Polymers including Ethynyl Groups

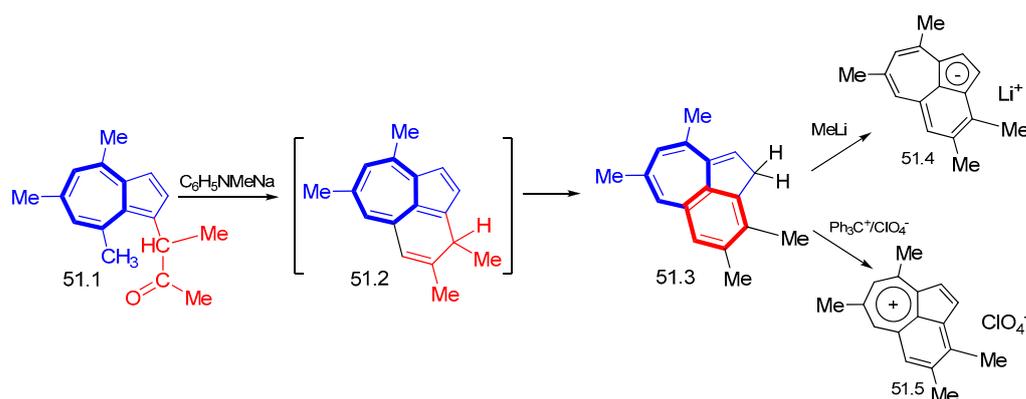
One of the remarkable properties of azulene is the possibility of being incorporated into a polymer chain with valuable technical properties. A recent review briefly presented a series of syntheses of such polymers and suggested their possible practical uses [70]. Among the azulene-containing polymers reported in this paper, 4,7-connected azulenes to each other or with various copolymers can be encountered, as well as other possible connections. Since, in the previous sub-chapter, several azulene compounds containing the ethynyl group were selected, a new family of polyazulenes connected through the seven-membered ring prepared by Sonogashira-coupling reactions will be presented here (Scheme 50) [71]. The compound 4,7-dibromoazulene **50.1** and the bis-ethynylazulene with substituents in the same positions, **50.2**, were connected under the Sonogashira reaction conditions by Murai et al. [71], and the polymer **50.3** resulted in a good yield. The same paper described the formation of the polymer **50.4** by the homopolymerization of azulenes using the Yamamoto protocol. Stille coupling was also realized, starting with the same dibromoazulene and 2,2'-(6-dodecylazulene-4,7-diyl)dithiophene, **50.5**, converted into a trimethylstannyl derivative. A more extensive presentation of the polyazulenes topic is beyond the scope of this review.



**Scheme 50.** Substitution with the simultaneous generation of a heteroaromatic substituent.

## 8. Polycyclic Compounds That Include the Azulenic System

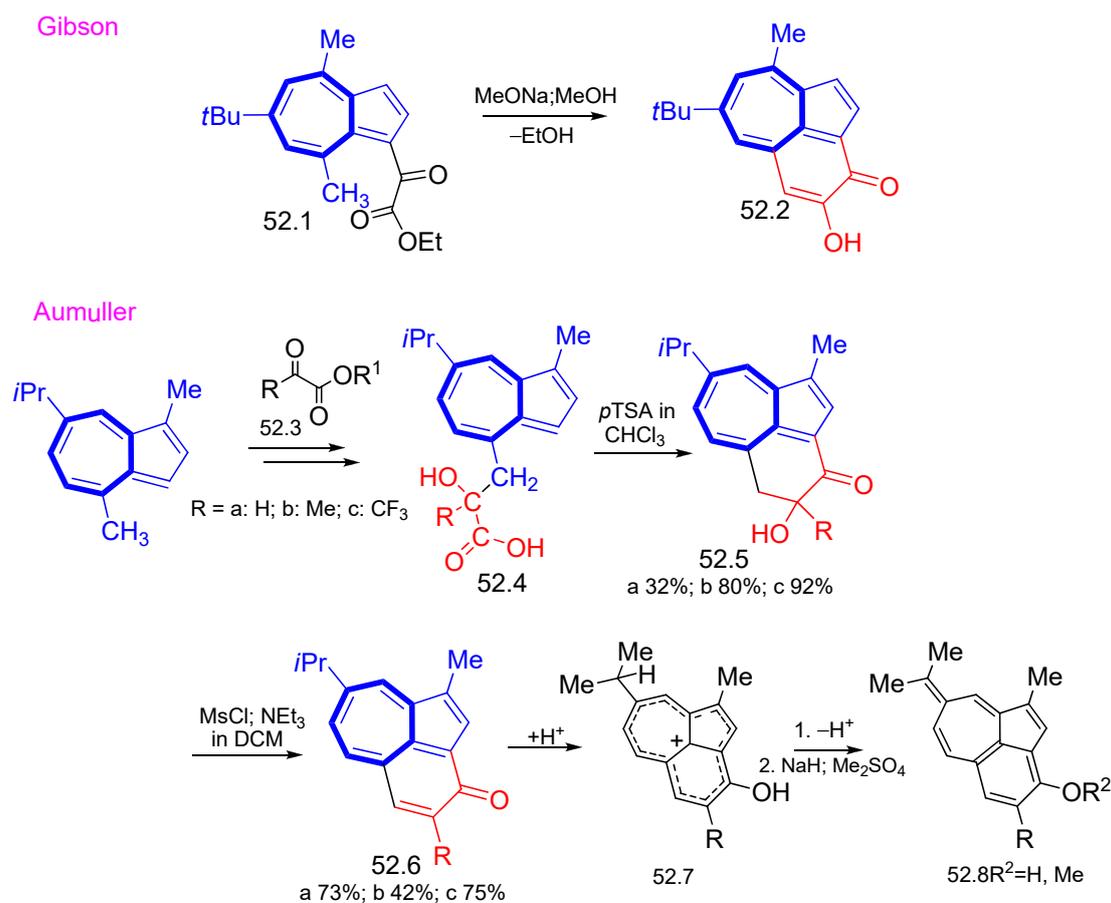
One of the earliest syntheses of a tricyclic compound in which azulene is present was performed by Hafner in 1963 [72,73]. As can be seen from Scheme 51, the internal addition of a carbanion to the C=O bond in ketone **51.1** followed by water elimination afforded the azulenic intermediate **51.2** including a cyclohexadiene system. However, because the stability of the benzene structure exceeds that of the nonalternant nonbenzenoid aromatic azulene, the benzenoid structure was adopted for the final benzoheptafulvene derivative **51.3**. A remarkable property of compound **51.3** consists of its ability to lose a proton, generating compound **51.4**, containing the stable cyclopentadienyl anionic structure. The same compound can be protonated to form the stable tropylium system contained in **51.5**.



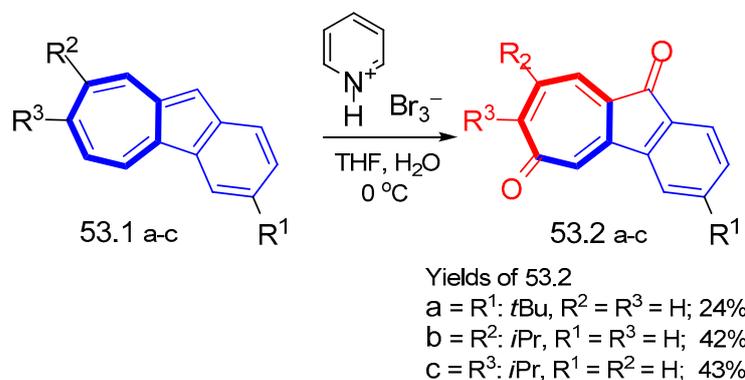
**Scheme 51.** The synthesis of the tricyclic compound **51.3** and its subsequent reactions.

The benzo[cd]azulen-3-ones **52.2** and **52.6** that will be discussed next are related to compound **51.2** reported by Hafner. Compound **52.2** was described by Gibson who obtained it by internal addition of a carbanion to the C=O bond in ketone **52.1** (Scheme 52) [74]. Later, the same system as in benzo-[cd]azulen-3-ones, **52.6**, was synthesized starting with an internal attack at Position 3 of compound **52.4** and the subsequent conversion of the intermediate 4,5-dihydrobenzo-[cd]azulen-3-ones, **52.5**. The latter transformation was realized by mesylation of the hydroxyl groups followed by base-assisted elimination of the mesylate in the presence of triethylamine (TEA) (Scheme 52) [75]. The obtained compound **52.6** was investigated in relation to its possible tautomerization. Thus, its protonation leads to a remarkable intermediate, **52.7**, with the benzo-[cd]azulenium cationic structure showing a continuous electronic conjugation. The elimination of the proton occurs at the *i*Pr group in **52.7** afforded the tautomer of **52.6** namely the compound **52.8** ( $\text{R}^2 = \text{H}$ ) where the azulene structure is lost in favor of the formation of the benzene moiety. The low stability of **52.8** ( $\text{R}^2 = \text{H}$ ) suggested it being obtained simultaneously with the methylation of the hydroxyl group with the generation of compound **52.8** ( $\text{R}^2 = \text{Me}$ ).

Benz[a]azulenes, **53.1** (Scheme 53), are somewhat related to the previously discussed tricyclic systems shown in Scheme 52 and have been studied as starting materials in oxidation reactions. These compounds, known for a long time but obtained advantageously recently by Shoji et al. starting from 2H-cyclohepta[b]furan-2-ones [76], were oxidized with bromine in a reaction performed by Nozoe et al. [77] or with  $\text{MnO}_2$  as reported by Sigrist and Hansen [78]. In these reactions, the participation of the azulene seven-atom ring in the formation of benz[a]azulenequinones, **53.2**, was highlighted. Considering the toxicity of bromine and the poor results when  $\text{MnO}_2$  was used as oxidant, as well as the complexity of the reaction mixture obtained in these reactions, Shoji et al. [79] used pyridinium hydrobromide perbromide as an oxidant with acceptable results, as described in Scheme 53.

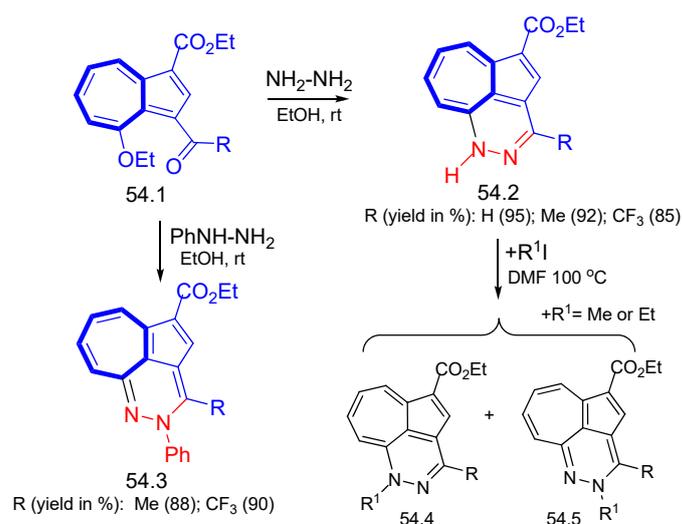


**Scheme 52.** The synthesis of tricyclic compound 52.6 and its tautomerization.



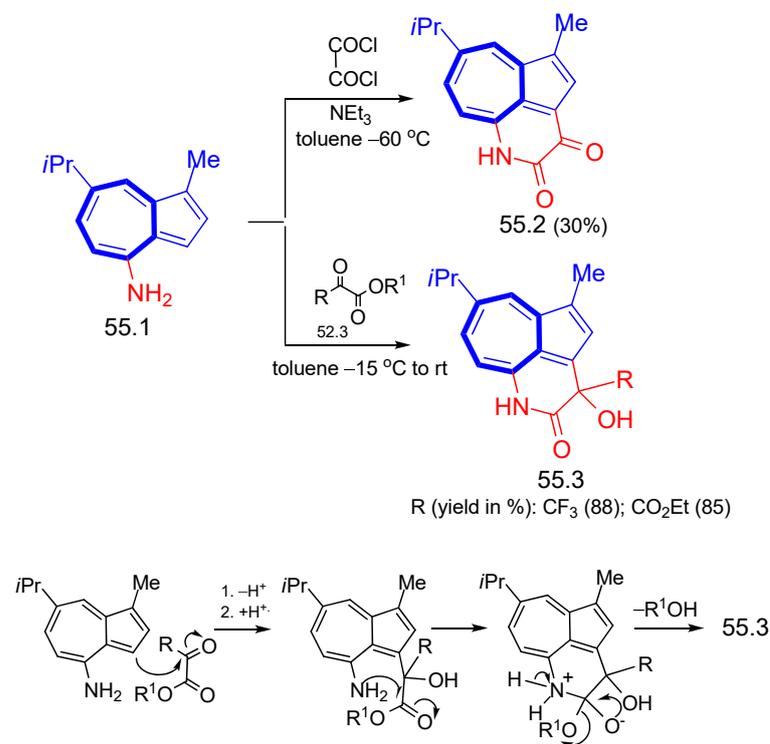
**Scheme 53.** Oxidation of benz[a]azulenes with pyridinium hydrobromide perbromide.

The azulenic tricyclic compounds can also contain a heterocyclic system. Among the compounds described in the literature, only two will be retained for exemplification. The ethyl 1H-azuleno [8,1-cd]-pyridazine-5-carboxylate, **54.2**, resulted in the reaction of ethyl 4-ethoxy-3-formylazulene-1-carboxylate, **54.1**, with hydrazine (Scheme 54). Presumably, the reaction occurred via a substitution reaction and subsequent intramolecular condensation [80]. By replacing hydrazine with phenylhydrazine, the fulvenic compound **54.3** was formed as a product. It is interesting that the alkylation of compound **54.2** with alkyl iodides led to a mixture of N-alkylated pyridazines and/or fulvene products, **54.4** and **54.5**.



**Scheme 54.** Synthesis of pyridazines and/or fulvenes starting from ethyl 4-ethoxy-3-formylazulene-1-carboxylate and hydrazines.

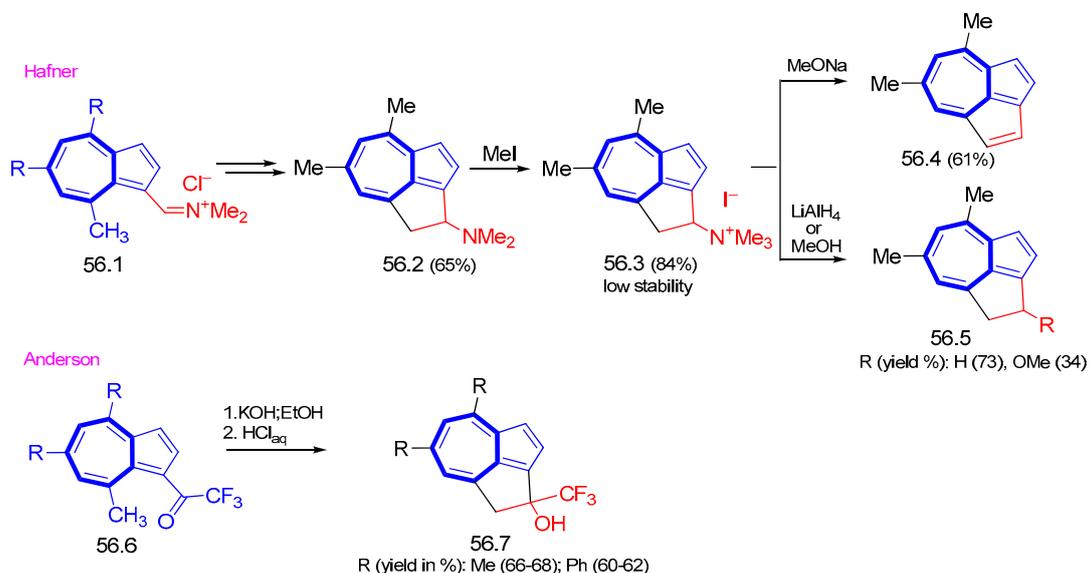
Other tricyclic compounds were obtained starting from the 4-aminoguaiazulene 55.1 which was reacted with 1,2-dicarbonyl compounds: oxalyl dichloride and compounds 52.3 (ethyl 3,3,3-trifluoro-2-oxopropanoate or diethyl 2-oxomalonate) [81]. The lactames 55.2 and 55.3 were formed in a cascade mechanism proposed by the authors and represented in Scheme 55.



**Scheme 55.** Tricyclic compounds obtained starting from 4-aminoguaiazulene and 1,2-dicarbonyl compounds.

The examples of tricyclic compounds discussed above referred to compounds in which azulene was condensed with a six-atom ring. In the following, certain procedures will be given for the realization of tricyclic azulenic systems containing a five atoms ring which are interesting both from a structural and historical point of view. After the synthesis of compound 56.1 by Vilsmeier–Haack reaction and the subsequent cyclization, Hafner

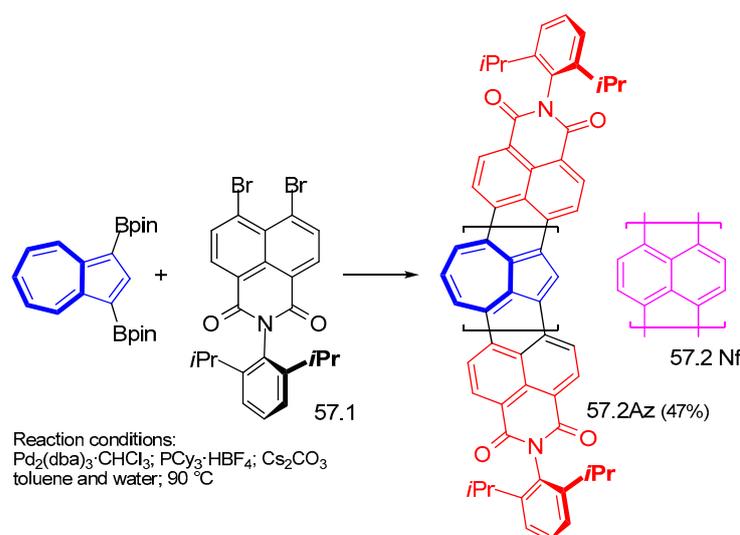
obtained the tricyclic amine **56.2** [82]. The ammonium salt **56.3** resulted by methylation was transformed into the compounds **56.4** and **56.5**, as resulted from Scheme 56.



**Scheme 56.** Tricyclic azulenic systems containing a five-atom ring.

Anderson et al. condensed the carbonyl group of the starting ketone **56.6** with the methyl of the seven-membered ring in a basic medium [83] and afforded the product **57.7** with various substituents at the seven-membered ring (Scheme 56).

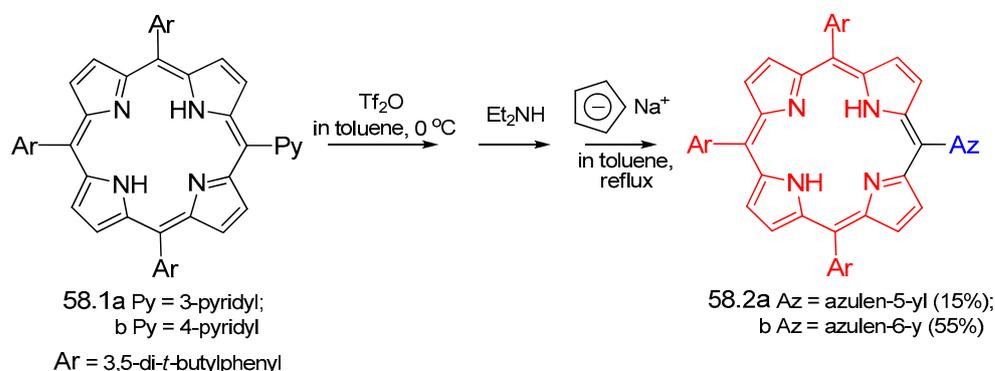
From the polycyclic aromatic hydrocarbons, special attention was paid to dicarboximides, which are valuable from a scientific point of view but also as new  $\pi$  scaffolds materials. After developing the synthesis procedure for the terylene-bis imide **57.2Nf**, with the structure partially represented in Scheme 57 [84] (naphthalene replaces azulene in the formula **57.2Az**), the same research team extended the concern to the replacement of naphthalene with azulene as in the compound **57.2Az** [85]. The last non-alternant isomer of the terylene-bis imide was synthesized in a moderate yield by the palladium-catalyzed annulation of the bis boronic ester of azulene and dibromide **57.1**.



**Scheme 57.** Synthesis of dicarboximides polycyclic aromatic hydrocarbons, terylene, and the azulenic isomer.

## 9. Porphyrinogenic Systems and Phthalocyanines Containing Azulenyl Moiety (Azulenocyanine)

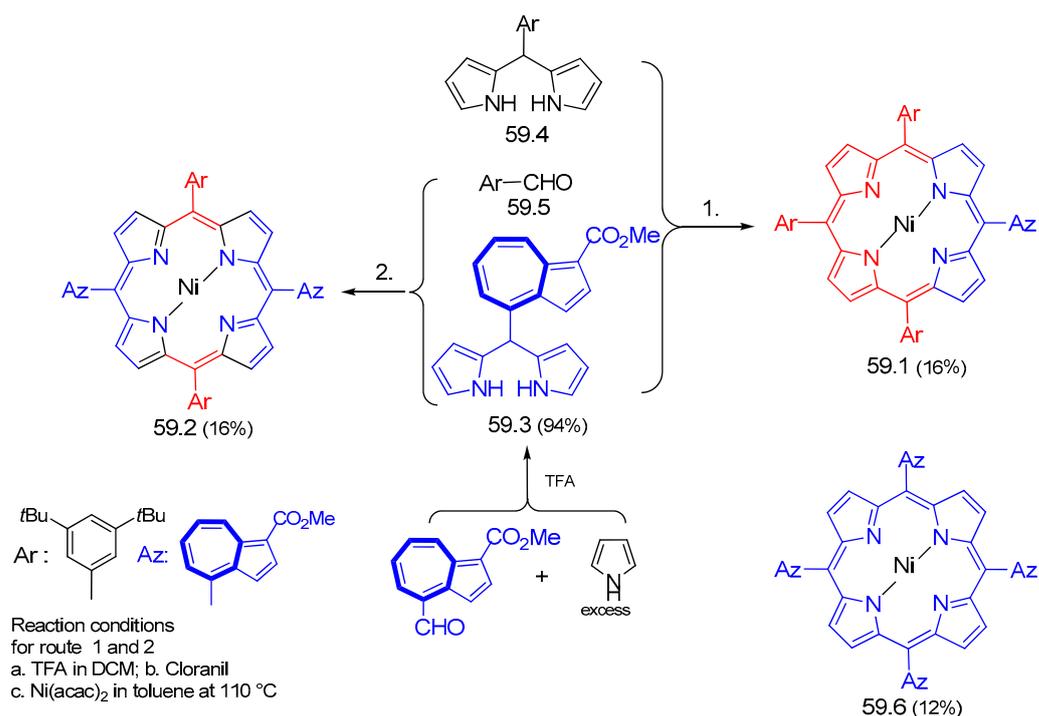
A fascinating chapter in azulene chemistry deals with the study of porphyrins with an extended electronic system by substituting them with an azulenyl group. The research of Kurotobi et al. realized the substituted porphyrinogenic systems with one to four azulenyl substituents linked with their different carbon atoms [86]. These research works differ from those of Sprutta and Lash, who introduced the azulene system into the porphyrin network [87–89]. In the following, the molecules in which the azulenyl moiety is *meso*-linked to the porphyrin system at the five- or six-atom ring will be considered. However, it must be remembered that Kurotobi et al. also synthesized porphyrins substituted with one azulen-1-yl or azulen-2-yl by the Suzuki–Miyaura coupling of *meso*-bromoporphyrin [86]. The first synthesis proposed by Kurotobi is based on the Ziegler–Hafner route to build the azulenic system that uses the pyridine ring as the starting system [86] (Scheme 58). The same research team, in a similar way, realized the compound with a porphyrin core substituted with four azulen-6-yl moieties; however, this was only present in a 1% yield.



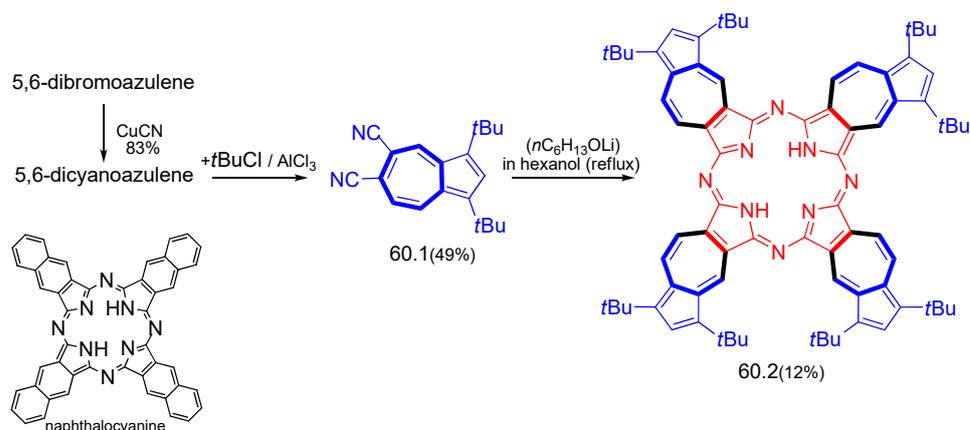
Scheme 58. Azulenyl moiety *meso*-linked to the porphyrin system.

The second synthesis is focused on the variation in the number of azulenes substituted at the Ni<sup>II</sup> porphyrinic system [32]. The procedure starts from the building of a porphyrinic system using azulene-containing molecules as depicted in Scheme 59. Metalization was realized upon treatment with Ni(acac)<sub>2</sub>. The scheme shows the obtainment of Ni<sup>II</sup>-5-(4-azulenyl)porphyrin, **59.1**, and Ni<sup>II</sup>-5,15-bis(4-azulenyl)porphyrin, **59.2**. The starting dipyrromethane **59.3** used for building compound **59.2** (Route 2) was obtained by the reaction of 4-azulencarbaldehyde with pyrrole in excess, in a good yield. The dipyrromethane **59.3** together with the dipyrromethane **59.4** and aldehyde **59.5** afforded the porphyrinic precursor of **59.1** (Route 1). Ni<sup>II</sup>-5,10,15,20-tetrakis(4-azulenyl)porphyrin, **59.6**, was prepared as a mixture of atropisomers under Lindsey conditions [90] from pyrrole and 4-azulencarbaldehyde. The authors also produced the azulene-fused porphyrin by binding the azulene in Position 2 with the pyrrole system belonging to the porphyrin skeleton [86].

Along with azuliporphyrins and azulenylporphyrins, a new family of dyes named phthalocyanines have shown intense near-IR absorption: a property that, together with a high stability to light and heat, can determine the use of these compounds in a series of technical applications. The azulenocyanine, named by the authors as the azulene-fused tetraazaporphyrin, **60.2** [91], is an isomer of naphthalocyanine synthesized in 1927 by de Diesbach et al. [92]. The synthesis begins with the two-step preparation of di-*tert*-butyl 5,6-dicyanoazulenes, **60.1**, which, in the presence of lithium alcoholate, generate azulenocyanine with a relatively low yield (Scheme 60).



**Scheme 59.** Ni<sup>II</sup>-porphyrin substituted with azulene-4-yl group(s).



**Scheme 60.** Synthesis of azulenocyanine.

## 10. Conclusions

The second part of the article *Azulene, Reactivity, and Scientific Interest Inversely Proportional to Ring Size* deals with the chemical behavior of the seven-atom azulenic ring. For a long time, researchers' concerns have focused on the chemical behavior of the five-atom azulenic ring. The electrophilic substitutions or cross-coupling reactions at this ring have been investigated and reported extensively, including in Part 1 of this review. The scientific interest shown in the chemical properties of the seven-atom ring, as well as the importance of certain obtained products which involve this ring in a series of practical uses, has boosted the study of the preparation and reactions of that system. The low charge density at the seven-atom ring favors nucleophilic attacks both directly on the ring and on certain substituents placed in appropriate positions. All these variants have been exemplified in the review. However, at the beginning, certain electrophilic reactions at this ring favored by the special structure of certain azulenic compounds have also been exemplified. Alongside nucleophilic attacks, reactions with organometallic derivatives, Stille, Heck–Negishi, and Suzuki–Miyaura cross-coupling, or the obtaining of azulene derivatives containing ethynyl group(s) have been reviewed here. The syntheses of tricyclic

products including the azulenic system in the skeleton, together with certain syntheses of polymers and copolymers containing azulenic units, were also briefly discussed. As in the previous review, synthesis schemes in which reaction conditions and yields are found have been preferred to an extended discussion about the schemes. This way of treating the material makes it easier to go through it or to find a particular synthesis procedure. The bibliographic references are focused both on recent information and on several pieces of experimental data that allow a useful foray into the progress of azulene chemistry.

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