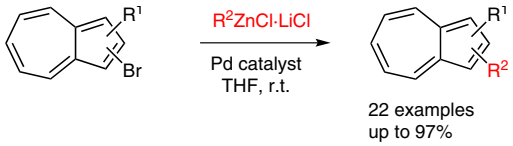
Synthesis J. Dubovik, A. Bredihhin Paper

A Convenient Synthesis of Functionalized Azulenes via Negishi Cross-Coupling



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Abstract A mild and effective method for the synthesis of functionalized azulenes is described. Negishi cross-coupling of bromoazulenes with functionalized aromatic, heterocyclic, benzylic, and alkylic organozinc reagents affords substituted azulenes in good yields. Functional groups, including ethoxycarbonyl, cyano, methoxy, fluoro, chloro, and bromo are well tolerated. Additionally, a one-pot procedure for introducing two different substituents into positions 1 and 3 of azulene through cross-coupling reaction is described for the first time.

Key words azulene, cross-coupling, halogenation, heterocycles, organometallic reagents

Azulene is an aromatic, bicyclic compound with a unique structure, which gives azulene a deep blue color, a strong dipole moment[1] (1.08 D), and unusual chemical properties. Azulene derivatives are common in nature (Figure 1) and are found in chamomile[2] (*Matricaria recutita*), trees[3] (*Bulnesia sarmientoi*), and certain mushrooms, such as saffron milk cap[4] (*Lactarius deliciosus*) and indigo milk cap[5] (*Lactarius indigo*).

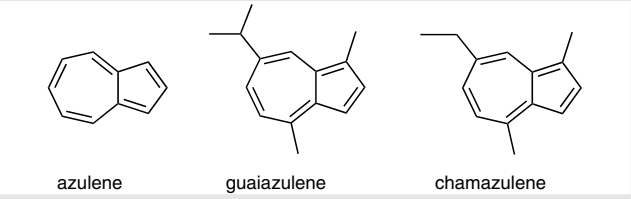


Figure 1 Azulene and its natural compounds

Azulene derivatives possess a broad range of biological activities, including anti-inflammatory,[6] antiulcer,[7] and anticancer[8,9] properties. Also, an azulene derivative HNS-32 has attracted attention as a coronary relaxant.[10] Recently, another derivative was investigated as a dopamine D4 receptor agonist for the treatment of erectile dysfunction and exhibited promising results.[11] Additionally, azulene derivatives have attracted attention in material science.[12,13]

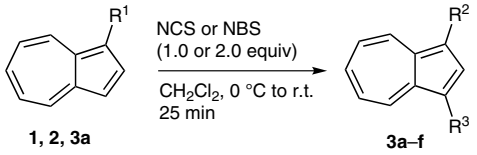
However, despite considerable interest of scientists and recent advances in azulene chemistry, the synthesis of azulene derivatives remains a difficult task. Often, it requires a multistep synthesis or even the synthesis of an azulene skeleton that already contains the desired substituent. Low stability of many haloazulenes and the sensitivity of azulene core towards organometallic reagents significantly limits the use of cross-coupling reactions. To date, mainly Suzuki[14] and Stille[12,15] couplings were used for the derivatization of azulene, often requiring prolonged reaction times and harsh reaction conditions. For example, the synthesis of 1,3-bis[*N*-(*tert*-butoxycarbonyl)-2-pyrrolyl]azulene through Stille coupling required 72 hours at 110 °C[15a] and the synthesis of 1,3-diphenylazulene through Suzuki coupling required 2 hours at 110 °C.[14a] Alkynes can be successfully introduced into azulene core by Sonogashira coupling.[16] Also some promising results were recently reported by Morita et al. using Kumada coupling.[17]

Taking into account the interesting properties of azulenes, it would be important to develop a method for the introduction of complex substituents bearing sensitive functional groups into azulene moiety and thus to increase availability of such derivatives for further studies. We consider Negishi reaction is more suitable for this purpose than Suzuki coupling because of much milder reaction conditions. However, Negishi cross-coupling has been rarely applied for derivatization of azulenes and only few examples, such as the alkylation of 6-bromoazulenes[18] and the synthesis of 1,3-di(2-pyridyl)azulene[19] are reported to date. Simple and nonfunctionalized substituents were used in these studies. To the best of our knowledge no reports con-

cerning the usage of functionalized organozinc reagents for derivatization of azulene through Negishi cross-coupling has been published.

We began our research with the synthesis of haloazulenes as substrates for Negishi cross-coupling. Chlorination and bromination of azulene (**1**) are usually performed in hexane or benzene and require 24 hours to complete.[14a,20] Simply changing the solvent to CH_2Cl_2 results in a dramatic reduction in the reaction time and gives excellent yields (Table 1).

Table 1 Halogenation Experiments



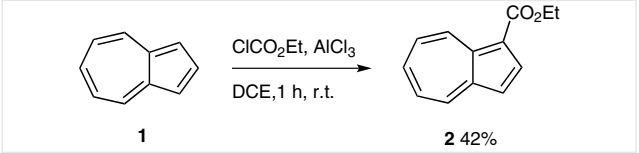
1, 2, 3a **3a–f**

Product	R^1	R^2	R^3	Yield (%)
3a	H	Cl	H	92
3b	H	Cl	Cl	91
3c	H	Br	H	53
3d	H	Br	Br	98
3e	Cl	Cl	Br	99
3f	CO_2Et	CO_2Et	Br	97

Monohalogenation of azulene (**1**) can be easily achieved by using one equivalent of NCS or NBS. Additionally, ethyl azulene-1-carboxylate (**2**) and 1-chloroazulene (**3a**) were easily halogenated to the corresponding bromo derivatives **3e** and **3f**, respectively, using NBS in excellent yields. Usage of two equivalents of halogenating agent results selectively in the 1,3-dihalogenated azulenes **3b** and **3d**, respectively. In the case of **3c**, standard halogenation procedure results in a 1:1 mixture of starting azulene (**1**) and 1,3-dibromoazulene (**3d**). However, evaporation of the reaction mixture on a rotary evaporator (40 °C, 5 min) yields **3c** as the main product.

Compounds **3a** and **3c** are known to be unstable.[20a] In our hands, neat **3a** was stable for hours at room temperature and for several months at –20 °C. In contrast, the lifetime of neat **3c** may be as short as few minutes at room temperature. To overcome the instability of **3c**, it was stored as a solution in petroleum ether. 2-Bromoazulene (**3g**) was synthesized according to the reported procedure.[16a]

Ethyl azulene-1-carboxylate (**2**) was synthesized directly from **1** and ethyl chloroformate in the presence of $AlCl_3$ in 42% yield (Scheme 1). Also 57% of the starting material **1** was recovered. This reaction does not proceed to completion even if excess of $AlCl_3$ and ethyl chloroformate are used. Previously, the synthesis of **2** required a multistep procedure and proceeded via trifluoacetylation, basic hydrolysis, and etherification.[21]

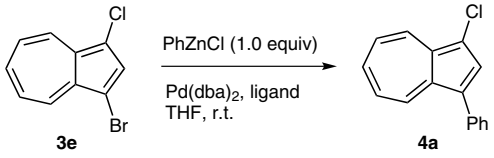


1 **2** 42%

Scheme 1 Synthesis of ethyl azulene-1-carboxylate (**2**)

The influence of different ligands on the Negishi cross-coupling reaction of 3-bromo-1-chloroazulene (**3e**) with PhZnCl (Table 2) was investigated. The reaction, in which triphenylphosphine was used as a ligand, did not proceed at room temperature, and only traces of the desired product were observed after 24 hours. Stirring the reaction mixture at 50 °C for 24 hours gave **4a** in 75% yield. In contrast, when SPhos[22] (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) was used as a ligand, the reaction was complete in 45 minutes at room temperature. In both cases, PnZnCl·LiCl was obtained through the insertion of magnesium into PhI in the presence of LiCl and the subsequent transmetalation with $ZnCl_2$. It was previously reported that *i*-PrI can dramatically decrease the cross-coupling reaction time by changing the mechanism to radical pathway.[23] Therefore, cross-coupling was performed using PhZnCl·LiCl containing *i*-PrI, which was obtained through an I–Mg exchange reaction of PhI with *i*-PrMgCl·LiCl. The cross-coupling reaction was complete in 30 minutes, showing only a moderate decrease in the reaction time.

Table 2 Optimization of Catalytic System



3e **4a**

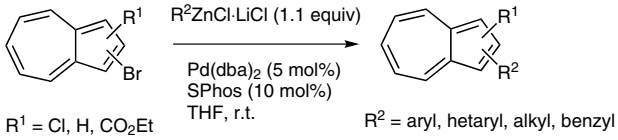
Entry	Catalytic system	Conditions	Yield (%)
1	$Pd(dba)_2$ (5 mol%), PPh_3 (20 mol%)	24 h, 50 °C	75
2	$Pd(dba)_2$ (5 mol%), SPhos (10 mol%)	45 min, r.t.	70
3	$Pd(dba)_2$ (5 mol%), SPhos (10 mol%), *i*-PrI	30 min, r.t.	76

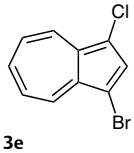
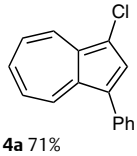
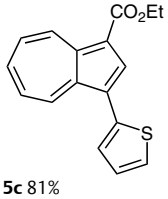
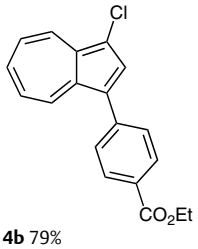
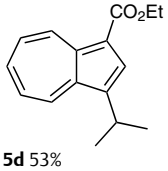
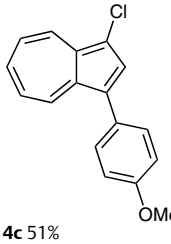
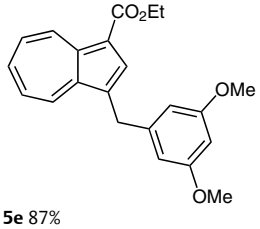
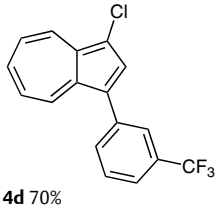
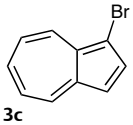
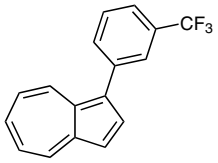
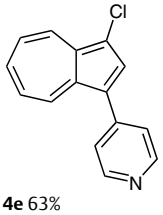
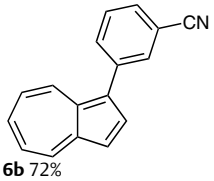
Most of the organozinc reagents were prepared from the corresponding iodides using an I–Mg exchange reaction with *i*-PrMgCl·LiCl (–20 °C, 30 min)[22] and subsequent transmetalation with $ZnCl_2$ because this approach is faster and more convenient than zinc-insertion reactions.

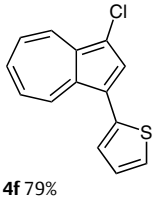
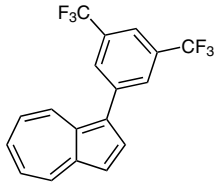
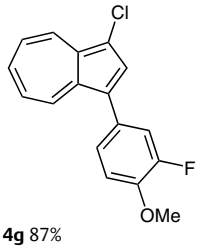
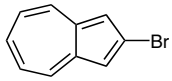
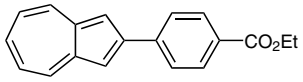
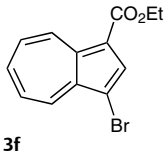
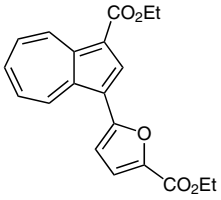
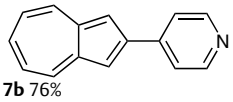
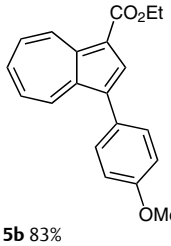
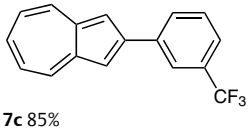
Aromatic substituents with sensitive functional groups were successfully introduced into azulene derivatives using Negishi cross-coupling (Table 3 and Table 4). Many functional groups, such as CO_2Et, CN, Cl, F, OMe, and CF_3, were tolerated. Most of the cross-coupling reactions proceeded

smoothly at room temperature in 0.5 to 1 hour; however, some reactions required up to 5 hours to reach completion (Table 3, entries 8 and 10).

Table 3 Negishi Cross-Coupling of Monobromoazulenes with Organozinc Reagents



Entry	Substrate	Time	Product	Entry	Substrate	Time	Product
1	 **3e**	0.5 h	 **4a** 71%	10	**3f**	5 h	 **5c** 81%
2	**3e**	0.5 h	 **4b** 79%	11	**3f**	1 h	 **5d** 53%
3	**3e**	0.5 h	 **4c** 51%	12	**3f**	2 h[a]	 **5e** 87%
4	**3e**	1 h	 **4d** 70%	13	 **3c**	1 h	 **6a** 80%
5	**3e**	1 h	 **4e** 63%	14	**3c**	3 h	 **6b** 72%

Entry	Substrate	Time	Product	Entry	Substrate	Time	Product
6	**3e**	2 h	 **4f** 79%	15	**3c**	4 h	 **6c** 65%
7	**3e**	1 h[a]	 **4g** 87%	16	 **3g**	1 h	 **7a** 86%
8	 **3f**	5 h[b]	 **5a** 62%	17	**3g**	1 h	 **7b** 76%
9	**3f**	2 h	 **5b** 83%	18	**3g**	0.5 h	 **7c** 85%

[a] 1.0 equiv of *i*-PrI was added.
[b] At 60 °C.

Reactions with aromatic substituents bearing electron-withdrawing group in *para*- and *meta*-positions gave good results (Table 3, entries 2, 4, 13, 14, 18). Thus, **4b** was obtained from **3e** in 30 minutes in 79% yield. Additionally, 3-trifluoromethylphenylzinc chloride was successfully coupled with **3e** to give **4d** in 70% yield. Substituents with electron-donating groups and a combination of electron-withdrawing and -donating groups were also successfully coupled (Table 3, entries 3, 7, 9). Thus, **5b** and **4g** were obtained in 83% and 87% yield, respectively; however, cross-coupling with **3e** resulted in **4c** only in moderate yield.

Heterocyclic substituents, including furan, thiophene, and pyridine, were successfully introduced into azulene (Table 3, entries 5, 6, 8, 10, 17). Thus, ethyl 5-bromofuran-2-carboxylate was treated with *i*-PrMgCl·LiCl, transmetalated with $ZnCl_2$, and successfully coupled with **3f** to give **5a**. Despite the presence of LiCl, which significantly improves the solubility of the organometallic reagents, thiophenylzinc chloride formed a precipitate and was used as a suspension. However, **4f** and **5c** were successfully obtained in 79% and 81% yield, respectively. Pyridine ring was readily introduced, resulting in **4e** and **7b** in good yields.

Furthermore, alkyl and functionalized benzylic substituents can be easily introduced (Table 3 entries 11, 12). Thus, isopropyl-substituted azulene **5d** was obtained in moderate yield. However, 3,5-dimethoxybenzylzinc chloride was successfully coupled to give **5e** in 87% yield.

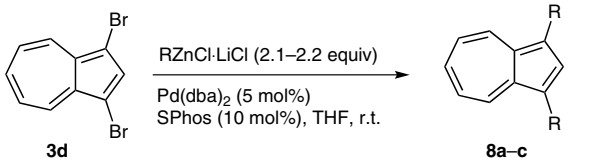
Several 1-substituted azulenes **6a–c** were obtained in good yields. Compounds of type **6** are difficult to prepare using other methods because of the instability of **3c** and the absence of the corresponding 1-metalated azulene. Azulenes **6** also have a reactive, unsubstituted position 3, which is available for further derivatization. The solution of **3c** in THF, which was used for cross-coupling reactions, was ob-

tained by evaporation of petroleum ether solution of **3c** under vacuum followed by the quick addition of anhydrous THF.

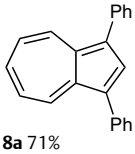
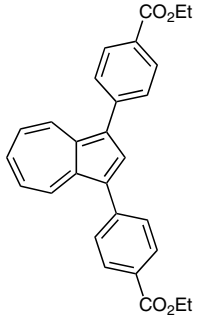
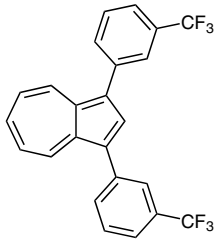
Derivatization of position 2 of the azulene core was also successfully performed. In this way, functionalized aromatic and pyridine substituents were introduced to furnish compounds **7a**–**c** in 76–86% yields. These compounds have the most reactive positions of the azulene core (1 and 3) free, which gives the possibility for their subsequent derivatization and synthesis of more complex structures.

Also both positions 1 and 3 of the azulene ring can be derivatized simultaneously with good to excellent yields using **3d** as starting material and two equivalents of the organozinc reagent (Table 4). Thus, **8b** was successfully obtained in 97% yield. Additionally, the Negishi cross-coupling of **3d** with phenylzinc and 3-trifluorophenylzinc chloride gave **8a** and **8c** in good yields.

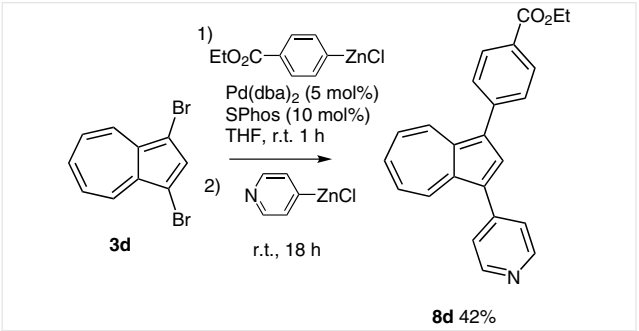
Table 4 Negishi Cross-Coupling of 1,3-Dibromoazulene (**3d**) with Organozinc Reagents



3d **8a–c**

Entry	Time	Product
1	0.5 h	 **8a** 71%
2	0.5 h	 **8b** 97%
3	0.5 h	 **8c** 62%

We also managed to introduce two different substituents to 1,3-dibromoazulene (**3d**) in a one-pot fashion (Scheme 2). First, 4-(ethoxycarbonyl)phenylzinc chloride (1.0 equiv) was added, and the reaction mixture was stirred for 1 hour. Then, 4-pyridylzinc chloride (1.0 equiv) was added and stirred overnight to give **8d** in 42% yield. This procedure allows the synthesis of a variety of complex substituted azulenes that are difficult to prepare or are completely inaccessible by other methods.



3d **8d** 42%

Scheme 2 One-pot introduction of two different substituents

In conclusion, we have developed a mild and effective method for the synthesis of highly functionalized azulene derivatives from bromoazulenes. The scope of this conversion was demonstrated using electron-poor and electron-rich aromatic, heterocyclic, alkylic, and benzylic substituents. This method showed high tolerance of sensitive functional groups and gave products in good yields. A variety of monobromoazulenes and 1,3-dibromoazulene were successfully derivatized using this method. We also provided a procedure for the introduction of two different substituents into positions 1 and 3 of the azulene in a one-pot fashion, which is an unprecedented result. A simple procedure for the synthesis of haloazulenes with excellent yields is also described.

All reactions with organometallic reagents were carried out under an argon atmosphere in dried (using a heat gun) glassware. The syringes that were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N_2. The $ZnCl_2$ solution was freshly prepared and stored under argon for not more than one week. Petroleum ether (PE) used refers to the fraction boiling in the 40–65 °C range. NMR spectroscopy was performed on a 400 MHz spectrometer using the residual solvent peak ($CDCl_3$, 7.26 ppm for ^1H and 77.16 ppm for ^{13}C spectra) as an internal standard. The IR spectra were recorded on an ATR module with a ZnSe crystal. The reactions were monitored using TLC and visualized with UV light. The products were purified using flash chromatography and silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM).

$ZnCl_2$ Solution in THF (1 M)

A 100 mL flask, equipped with a magnetic stirring bar and a septum, was charged with anhydrous $ZnCl_2$ (6.815 g, 50 mmol) and heated with a heatgun (350 °C, 15 min and 550 °C, 15 min) under high vacuum. After cooling to r.t., anhydrous THF (50 mL) was added and the stirring was continued until the salt was completely dissolved.

Ethyl Azulene-1-carboxylate (2)

Azulene (**1**; 1.282 g, 10 mmol) was dissolved in 1,2-dichloroethane (20 mL), then ethyl chloroformate (1.085 g, 10 mmol) followed by $AlCl_3$ (1.333 g, 10 mmol) were added to the solution at r.t. After the addition of $AlCl_3$, the reaction mixture warmed up and changed the color to red. The mixture was stirred for 1 h at r.t. Then, it was transferred to a separatory funnel, diluted with CH_2Cl_2 (50 mL), and washed with HCl (100 mL, 0.5 M) and H_2O (50 mL). The aqueous fractions were combined and back-extracted with CH_2Cl_2 (2 × 30 mL). The organic fractions were combined, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2) to afford **2** as a violet oil; yield: 841 mg (42%) and the starting azulene (727 mg).

IR (ATR, neat): 3028, 2978, 2932, 2901, 1682, 1420, 1396, 1211, 1173, 1142, 1038, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.2 Hz, 3 H), 4.45 (q, *J* = 7.2 Hz, 2 H), 7.28 (d, *J* = 4.3 Hz, 1 H), 7.39 (t, *J* = 9.7 Hz, 1 H), 7.52 (t, *J* = 9.9 Hz, 1 H), 7.75 (t, *J* = 9.7 Hz, 1 H), 8.39–8.43 (m, 2 H), 9.66 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 59.8, 117.2, 117.6, 126.6, 127.6, 137.8, 138.2, 138.9, 140.3, 140.7, 144.8, 165.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}O_2$: 201.0910; found: 201.0905.

Haloazulenes; 1-Chloroazulene (3a); Typical Procedure 1 (TP1)

NCS (1.335 g, 10 mmol) was added to a stirred solution of azulene (**1**; 1.282 g, 10 mmol) in CH_2Cl_2 (50 mL) at 0 °C and stirred for 10 min. Then, the cooling bath was removed, and the reaction mixture was stirred at r.t. for another 15 min. Next, the reaction mixture was evaporated to a small volume (~4 mL), and the residue was diluted with PE (30 mL). As a result, a precipitate of succinimide formed and was filtered off. Then, the procedure was repeated once more. The volatiles were evaporated, and the residue was purified by column chromatography (eluent: PE) to afford **3a** as a blue oil; yield: 1.488 g (92%).

IR (ATR, neat): 3078, 3048, 3024, 2959, 1578, 1481, 1389, 1281, 925, 867, 764, 729, 563, 545 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.24 (m, 2 H), 7.32 (d, *J* = 4.3 Hz, 1 H), 7.63 (t, *J* = 9.9 Hz, 1 H), 7.79 (d, *J* = 4.3 Hz, 1 H), 8.26 (d, *J* = 9.3 Hz, 1 H), 8.40 (d, *J* = 9.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.9, 116.6, 123.0, 123.5, 133.5, 134.6, 135.1, 137.7, 138.9, 139.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_8Cl$: 163.0309; found: 163.0303.

1,3-Dichloroazulene (3b)

According to TP1, NCS (267 mg, 2.0 mmol) was reacted with azulene (**1**; 128 mg, 1.0 mmol) to give, after purification by column chromatography (eluent: PE), **3b** as green needles; yield: 179 mg (91%); mp 91–92 °C (Lit.[20a] mp 87–88 °C).

IR (ATR, neat): 3102, 3051, 3021, 2955, 2924, 2855, 1578, 1489, 1478, 1389, 1308, 1292, 1146, 1092, 941, 845, 787, 725, 613, 594, 567 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 9.9 Hz, 2 H), 7.60–7.65 (m, 2 H), 8.30 (d, *J* = 9.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.7, 123.5, 132.7, 133.2, 135.4, 140.4.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_6Cl_2$: 195.9847; found: 195.9835.

1-Bromoazulene (3c)

According to TP1, NBS (178 mg, 1.0 mmol) was reacted with azulene (**1**; 128 mg, 1.0 mmol) to give, after purification by column chromatography (eluent: PE), **3c** as a blue oil; yield: 109 mg (53%).

IR (ATR, neat): 3078, 3048, 3021, 2955, 1578, 1477, 1389, 1292, 1273, 914, 856, 764, 729, 559 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.12 (t, *J* = 9.8 Hz, 1 H), 7.19 (t, *J* = 9.8 Hz, 1 H), 7.29 (d, *J* = 4.2 Hz, 1 H), 7.56 (t, *J* = 9.9 Hz, 1 H), 7.80 (d, *J* = 4.2 Hz, 1 H), 8.19 (d, *J* = 9.5 Hz, 1 H), 8.32 (d, *J* = 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.1, 117.1, 123.4, 123.7, 135.4, 136.1, 137.3, 137.9, 138.8, 140.1.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_7Br$: 205.9731; found: 205.9721.

1,3-Dibromoazulene (3d)

According to TP1, NBS (3.560 g, 20 mmol) was reacted with azulene (**1**; 1.282 g, 10 mmol) to give, after purification by column chromatography (eluent: PE), **3d** as dark-blue crystals; yield: 2.790 g (98%); mp 92–93 °C (Lit.[20a] mp 88–89 °C).

IR (ATR, neat): 3105, 3059, 2924, 2859, 1574, 1477, 1450, 1377, 1285, 930, 856, 764, 737, 590, 563 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 10.0 Hz, 2 H), 7.70–7.65 (m, 1 H), 7.81 (s, 1 H), 8.27–8.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.9, 124.2, 135.9, 136.8, 138.4, 140.2.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_6Br_2$: 283.8836; found: 283.8824.

1-Bromo-3-chloroazulene (3e)

According to TP1, NBS (1.629 g, 9.15 mmol) was reacted with **3a** (1.488 g, 9.15 mmol) to give, after purification by column chromatography (eluent: PE), **3e** as green needles; yield: 2.285 g (99%); mp 82–83 °C (Lit.[20a] mp 77.5–78 °C).

IR (ATR, neat): 3098, 3048, 3021, 2990, 2955, 2924, 2870, 1694, 1578, 1485, 1385, 1296, 941, 845, 775, 725, 594 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (dt, *J* = 2.6, 9.8 Hz, 2 H), 7.63 (t, *J* = 9.9 Hz, 1 H), 7.71 (s, 1 H), 8.25 (d, *J* = 9.7 Hz, 1 H), 8.29 (d, *J* = 9.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.8, 115.7, 123.7, 123.9, 134.0, 135.08, 135.11, 135.6, 137.1, 140.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_7BrCl$: 240.9414; found: 240.9410.

Ethyl 3-Bromoazulene-1-carboxylate (3f)

According to TP1, NBS (747 mg, 4.2 mmol) reacted with **2** (841 mg, 4.2 mmol) to give, after purification by column chromatography (eluent: CH_2Cl_2), **3f** as black crystals; yield: 1.1407 g (97%); mp 75–76 °C.

IR (ATR, neat): 3028, 2982, 2913, 2870, 1694, 1578, 1501, 1458, 1420, 1385, 1331, 1288, 1196, 1165, 1099, 1042, 980, 945, 887, 864, 772, 733, 607, 563 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 3 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 7.56–7.47 (m, 2 H), 7.81 (t, *J* = 10.0 Hz, 1 H), 8.32 (s, 1 H), 8.46 (dd, *J* = 1.1, 9.8 Hz, 1 H), 9.60 (dd, *J* = 0.9, 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 60.1, 104.4, 116.3, 127.1, 128.3, 137.6, 138.3, 140.0, 140.2, 140.3, 140.9, 164.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{12}BrO_2$: 279.0015; found: 279.0011.

Zn Reagents; from Iodobenzene; Typical Procedure 2 (TP2)

A flask was charged with *i*-PrMgCl·LiCl (4.63 mL, 1.0807 M) cooled to –20 °C, and then neat iodobenzene (1.020 g, 5 mmol) was added. The reaction mixture was stirred for 30 min, and then, a $ZnCl_2$ solution in THF (5.5 mL, 1 M) was added. The mixture was stirred for 15 min and allowed to warm to r.t. over 30 min. Titration with I_2 gave a concentration of 0.5226 M.

Negishi Cross-Coupling; 1-Chloro-3-phenylazulene (4a); Typical Procedure 3 (TP3)

A flask charged with **3e** (242 mg, 1 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), and SPhos (40 mg, 10 mol%) was evacuated and back-filled with argon, and then, THF (1.5 mL) was added, and the reaction mixture was stirred for 5 min. Next, the organozinc reagent PhZnCl (2.10 mL, 0.5226 M) was added, and the mixture was stirred for 30 min. The mixture was quenched with aq NH_4Cl (0.5 mL), diluted with Et_2O (30 mL), and the organic layer was washed with sat. aq NH_4Cl (2 × 30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography (eluent: CH_2Cl_2), to afford **4a** as green crystals; yield: 245 mg (79%); mp 76–77 °C.

IR (ATR, neat): 3036, 3021, 2959, 2924, 1574, 1485, 1393, 1350, 1296, 941, 849, 806, 764, 734, 702, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (t, *J* = 9.8 Hz, 1 H), 7.18 (t, *J* = 9.8 Hz, 1 H), 7.40 (tt, *J* = 1.5, 7.2 Hz, 1 H), 7.50–7.54 (m, 2 H), 7.57–7.63 (m, 3 H), 8.42 (dd, *J* = 0.7, 9.7 Hz, 1 H), 7.91 (s, 1 H), 8.47 (d, *J* = 9.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.6, 123.1, 123.9, 126.9, 128.8, 129.4, 129.9, 134.6, 134.76, 134.83, 135.1, 136.4, 136.6, 139.7.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{11}Cl$: 238.0549; found: 238.0540.

Ethyl 4-(3-Chloroazulen-1-yl)benzoate (4b)

The organozinc reagent was prepared from ethyl 4-iodobenzoate according to TP2 with a concentration of 0.3731 M. According to TP3, **3e** (242 mg, 1 mmol) was reacted with the organozinc reagent (2.95 mL, 0.3731 M) for 30 min to give, after purification by column chromatography (eluent: CH_2Cl_2), **4b** as green crystals; yield: 245 mg (79%); mp 107–108 °C.

IR (ATR, neat): 3024, 2986, 2905, 2870, 1717, 1605, 1578, 1389, 1350, 1273, 1173, 1103, 1026, 845, 806, 768, 741, 706, 610, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 3 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 7.15 (t, *J* = 9.8 Hz, 1 H), 7.21 (t, *J* = 9.8 Hz, 1 H), 7.60–7.65 (m, 3 H), 7.89 (s, 1 H), 8.11–8.21 (m, 2 H), 8.40 (dd, *J* = 0.9, 9.7 Hz, 1 H), 8.45 (d, *J* = 9.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 61.1, 117.0, 123.8, 124.6, 128.1, 128.6, 129.5, 130.1, 134.8, 134.9, 135.2, 135.4, 136.5, 140.0, 140.9, 166.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}ClO_2$: 311.0834; found: 311.0825.

1-Chloro-3-(4-methoxyphenyl)azulene (4c)

The organozinc reagent was prepared from 4-iodoanisole according to TP2 with a concentration of 0.5122 M. According to TP3, **3e** (242 mg, 1 mmol) was reacted with organozinc reagent (2.1 mL, 0.5122 M) for 30 min to give, after purification by column chromatography (eluent: PE), **4c** as green crystals; yield: 137 mg (51%); mp 77–78 °C.

IR (ATR, neat): 3040, 3017, 2959, 2932, 2847, 1609, 1574, 1524, 1485, 1450, 1389, 1350, 1285, 1238, 1169, 1107, 1034, 953, 941, 826, 802, 725, 629, 567, 529 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 7.03–7.10 (m, 3 H), 7.14 (t, *J* = 9.7 Hz, 1 H), 7.47–7.50 (m, 2 H), 7.58 (t, *J* = 9.8 Hz, 1 H), 7.85 (s, 1 H), 8.37 (dd, *J* = 1.0, 9.7 Hz, 1 H), 8.40 (dd, *J* = 0.7, 9.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 114.4, 116.4, 122.8, 123.6, 128.9, 129.2, 130.9, 134.3, 134.5, 134.8, 135.0, 136.6, 139.6, 158.9.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{13}ClO$: 268.0655; found: 268.0646.

1-Chloro-3-[3-(trifluoromethyl)phenyl]azulene (4d)

The organozinc reagent was prepared from 3-iodobenzotrifluoride according to TP2 with a concentration of 0.5088 M. According to TP3, **3e** (242 mg, 1 mmol) was reacted with organozinc reagent (2.2 mL, 0.5088 M) for 1 h to give, after purification by column chromatography (eluent: PE), **4d** as a green solid; yield: 216 mg (70%); mp 46–48 °C.

IR (ATR, neat): 3048, 3024, 2963, 2924, 1574, 1485, 1454, 1393, 1308, 1273, 1161, 1103, 1069, 964, 837, 799, 733, 691, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 9.8 Hz, 1 H), 7.23 (t, *J* = 9.8 Hz, 1 H), 7.58–7.73 (m, 4 H), 7.82 (s, 1 H), 7.89 (s, 1 H), 8.39 (dd, *J* = 0.5, 9.7 Hz, 1 H), 8.43 (dd, *J* = 0.8, 9.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.9, 123.5 (q, *J* = 3.7 Hz), 123.8, 124.6, 124.8 (q, *J* = 272.9 Hz), 126.4 (q, *J* = 3.9 Hz), 127.6, 129.3, 131.3 (q, *J* = 32.3 Hz), 133.0 (q, *J* = 1.5 Hz), 134.8, 135.0, 135.5, 136.3, 137.2, 140.0.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{10}ClF_3$: 306.0423; found: 306.0411.

4-(3-Chloroazulen-1-yl)pyridine (4e)

Organozinc reagent: A flask was charged with 4-iodopyridine (923 mg, 4.5 mmol), then THF (2 mL) was added, and the mixture was cooled to –20 °C. After the addition of *i*-PrMgCl·LiCl (4.2 mL, 1.0807 M), the cooling bath was removed and the reaction mixture was stirred for 1 h at r.t. After this, $ZnCl_2$ solution in THF (5.0 mL, 1 M) was added. The mixture was stirred for 15 min and titrated. Titration with I_2 gave a concentration of 0.3252 M.

Coupling reaction: A flask charged with **3e** (242 mg, 1 mmol), $Pd(dba)_2$ (30 mg, 5 mol%), and SPhos (40 mg, 10 mol%) was evacuated and back-filled with argon. THF (1.5 mL) was added and the reaction mixture was stirred for 5 min. Next, the organozinc reagent (3.4 mL, 0.3252 M) was added, and the mixture was stirred for 1 h. The mixture was quenched with H_2O (0.5 mL) and diluted with CH_2Cl_2 (30 mL). The organic layer was washed with aq NH_4Cl–NH_3 (25% in H_2O) (1:1 mixture, 2 × 30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), evaporated, and the residue was purified by chromatography (eluent: Et_2O) to afford **4e** as a green solid; yield: 151 mg (63%); mp 99–100 °C.

IR (ATR, neat): 3051, 3024, 2990, 2959, 2924, 2851, 1597, 1578, 1489, 1420, 1389, 1354, 1292, 1215, 991, 957, 826, 733, 675, 590, 571 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.19 (m, 2 H), 7.45–7.44 (m, 2 H), 7.67 (t, *J* = 9.8 Hz, 1 H), 7.89 (s, 1 H), 8.42 (dd, *J* = 1.1, 9.8 Hz, 1 H), 8.47–8.50 (m, 1 H), 8.67 (d, *J* = 4.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.3, 124.2, 124.3, 125.1, 125.9, 134.7, 135.0, 135.7, 136.2, 140.2, 143.9, 150.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}ClN$: 240.0575; found: 240.0573.

2-(3-Chloroazulen-1-yl)thiophene (4f)

The organozinc reagent was prepared from 2-iodothiophene according to TP2 with a concentration of 0.5655 M. According to TP3, **3e** (242 mg, 1 mmol) was reacted with the organozinc reagent (1.95 ml, 0.5655 M) for 2 h to give, after purification by column chromatography (eluent: PE), **4d** as a green solid; yield: 194 mg (79%); mp 67–68 °C.

IR (ATR, neat): 3105, 3071, 3021, 2974, 2862, 1574, 1493, 1454, 1393, 1350, 1296, 1219, 926, 849, 826, 733, 687, 570 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.19 (m, 3 H), 7.25 (dd, *J* = 1.1, 3.5 Hz, 1 H), 7.37 (dd, *J* = 1.3, 5.1 Hz, 1 H), 7.60 (t, *J* = 9.9 Hz, 1 H), 7.92 (s, 1 H), 8.35 (dd, *J* = 0.9, 9.7 Hz, 1 H), 8.65 (d, *J* = 9.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.9, 121.7, 123.6, 124.3, 125.1, 125.3, 127.9, 134.6, 134.8, 135.2, 135.3, 136.7, 138.4, 140.1.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{14}H_9ClS$: 244.0113; found: 244.0106.

1-Chloro-3-(3-fluoro-4-methoxyphenyl)azulene (4g)

The organozinc reagent was prepared by transmetalation of commercial 3-fluoro-4-methoxyphenylmagnesium bromide (5.6 mL, 0.5363 M) with $ZnCl_2$ solution in THF (3.3 mL, 1 M) in 15 min at r.t. Titration with I_2 gave a concentration of 0.3396 M. According to TP3, **3e** (242 mg, 1 mmol) was reacted with the organozinc reagent (3.2 mL, 0.3396 M) and *i*-PrI (0.10 mL, 1 mmol) for 1 h to give, after purification by column chromatography (eluent: PE), **4g** as green crystals; yield: 249 mg (87%); mp 85–86 °C.

IR (ATR, neat): 3051, 3005, 2963, 2932, 2839, 1574, 1528, 1497, 1439, 1393, 1296, 1265, 1215, 1126, 1026, 868, 810, 737, 605, 574 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 (s, 3 H), 7.06–7.26 (m, 4 H), 7.29 (dd, *J* = 2.1, 12.2 Hz, 1 H), 7.61 (t, *J* = 9.8 Hz, 1 H), 7.81 (s, 1 H), 8.39 (t, *J* = 8.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.6, 114.0 (d, *J* = 2.6 Hz), 116.5, 117.4 (d, *J* = 18.7 Hz), 123.3, 124.0, 125.5 (d, *J* = 3.3 Hz), 127.9 (d, *J* = 1.8 Hz), 129.7 (d, *J* = 7.0 Hz), 134.55, 134.57, 134.8, 135.3, 136.4, 139.8, 146.8 (d, *J* = 11.0 Hz), 151.4, 153.9.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{12}ClFO$: 286.0561; found: 286.0552.

Ethyl 5-[3-(Ethoxycarbonyl)azulen-1-yl]furan-2-carboxylate (5a)

The organozinc reagent was prepared from ethyl 5-bromofuran-2-carboxylate according to TP2 with a concentration of 0.3467 M. According to TP3, **3f** (279 mg, 1 mmol) was reacted with the organozinc reagent (2.3 mL, 0.4694 M) for 30 min to give, after purification by column chromatography (eluent: PE–Et_2O, 2:1), **5a** as black crystals; yield: 210 mg (62%); mp 120–122 °C.

IR (ATR, neat): 3059, 3028, 2978, 2932, 2905, 1705, 1686, 1532, 1423, 1373, 1300, 1204, 1146, 1115, 1037, 775, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.48 (m, 6 H), 4.41 (q, *J* = 7.2, 2 H), 4.44 (q, *J* = 7.2, 2 H), 6.76 (d, *J* = 3.6 Hz, 1 H), 7.31 (d, *J* = 3.6 Hz, 1 H), 7.55 (dt, *J* = 4.0, 9.8 Hz, 2 H), 7.83 (t, *J* = 9.8 Hz, 1 H), 8.65 (s, 1 H), 9.18 (d, *J* = 9.6 Hz, 1 H), 9.67 (d, *J* = 9.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 14.7, 60.2, 60.9, 108.0, 117.2, 117.6, 119.9, 128.6, 129.0, 138.2, 138.9, 139.1, 139.3, 140.6, 142.6, 143.4, 155.7, 159.1, 165.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}O_5$: 339.1227; found: 339.1218.

Ethyl 3-(4-Methoxyphenyl)azulene-1-carboxylate (5b)

The organozinc reagent was prepared from 4-iodoanisole according to TP2 with a concentration of 0.5122 M. According to TP3, **3f** (279 mg, 1 mmol) was reacted with the organozinc reagent (2.2 mL, 0.5122 M) for 4 h to give, after purification by column chromatography (eluent: CH_2Cl_2), **5b** as black crystals; yield: 253 mg (83%); mp 113–114 °C.

IR (ATR, neat): 3040, 2978, 2932, 2905, 2835, 1686, 1528, 1504, 1427, 1389, 1246, 1207, 1173, 1030, 980, 837, 775, 745, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, *J* = 7.2 Hz, 3 H), 3.89 (s, 3 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 7.03–7.07 (m, 2 H), 7.36 (t, *J* = 9.8 Hz, 1 H), 7.47–7.53 (m, 3 H), 7.75 (t, *J* = 9.8 Hz, 1 H), 8.44 (s, 1 H), 8.58 (dd, *J* = 0.8, 9.8 Hz, 1 H), 9.68 (dd, *J* = 0.8, 9.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 55.5, 59.9, 114.3, 116.0, 126.7, 127.5, 129.1, 130.6, 130.9, 137.0, 138.1, 139.6, 140.0, 140.2, 141.4, 158.9, 165.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}O_3$: 307.1329; found: 307.1323.

Ethyl 3-(Thiophen-2-yl)azulene-1-carboxylate (5c)

The organozinc reagent was prepared from 2-iodothiophene according to TP2 with a concentration of 0.5655 M. According to TP3, **3f** (279 mg, 1 mmol) was reacted with the organozinc reagent (1.95 mL, 0.5655 M) for 5 h to give, after purification by column chromatography (eluent: PE–Et_2O, 3:1), **5c** as black crystals; yield: 230 mg (81%); mp 93–95 °C.

IR (ATR, neat): 3102, 3067, 2978, 2932, 2901, 1686, 1446, 1420, 1389, 1196, 1157, 1041, 826, 775, 741, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.2 Hz, 3 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 7.19 (dd, *J* = 3.7, 5.1 Hz, 1 H), 7.28 (dd, *J* = 1.1, 3.5 Hz, 1 H), 7.39 (dd, *J* = 1.1, 5.1 Hz, 1 H), 7.44 (t, *J* = 9.8 Hz, 1 H), 7.52 (t, *J* = 9.7 Hz, 1 H), 7.79 (t, *J* = 9.8 Hz, 1 H), 8.51 (s, 1 H), 8.84 (d, *J* = 9.9 Hz, 1 H), 9.67 (d, *J* = 9.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 60.1, 116.4, 123.1, 125.2, 125.6, 127.3, 127.8, 128.1, 137.2, 138.5, 140.0, 140.1, 140.4, 141.9, 165.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}O_2S$: 283.0788; found: 283.0782.

Ethyl 3-Isopropylazulene-1-carboxylate (5d)

The organozinc reagent was prepared by transmetalation of the commercial *i*-PrMgCl·LiCl (5.4 mL, 1.1202 M) with $ZnCl_2$ solution in THF (6.6 mL, 1 M) in 15 min at r.t. Titration with I_2 gave a concentration of 0.5535 M. According to TP3, **3f** (279 mg, 1 mmol) was reacted with the organozinc reagent (2.0 mL, 0.5535 M) for 1 h to give, after purification using column chromatography (eluent: PE–Et_2O, 4:1), **5d** as a violet oil; yield: 129 mg (53%).

IR (ATR, neat): 3028, 2959, 2932, 2870, 1686, 1454, 1427, 1385, 1200, 1169, 1138, 1038, 775, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41–1.48 (m, 10 H), 3.55 (sept, *J* = 6.8 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 7.37 (t, *J* = 9.9 Hz, 1 H), 7.45 (t, *J* = 9.9 Hz, 1 H), 7.73 (t, *J* = 9.9 Hz, 1 H), 8.32 (s, 1 H), 8.44 (d, *J* = 9.9 Hz, 1 H), 9.60 (d, *J* = 9.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 24.4, 26.1, 59.8, 115.6, 125.4, 127.0, 134.4, 137.1, 137.2, 137.5, 138.8, 140.0, 141.1, 165.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{19}O_2$: 243.1380; found: 243.1373.

Ethyl 3-(3,5-Dimethoxybenzyl)azulene-1-carboxylate (5e)

The organozinc reagent was prepared by transmetalation of commercial 3,5-dimethoxybenzylmagnesium chloride solution (22.6 mL, 0.1327 M) with $ZnCl_2$ solution in THF (3.3 mL, 1 M) in 15 min at r.t. Titration with I_2 gave a concentration of 0.1218 M. According to TP3, **3f** (279 mg, 1 mmol) was reacted with the organozinc reagent (9.0 mL, 0.1218 M) for 2 h to give, after purification by column chromatography (eluent: PE–Et_2O, 4:1), **5e** as dark-violet crystals; yield: 322 mg (92%); mp 103–105 °C.

IR (ATR, neat): 2955, 2932, 2835, 1682, 1593, 1458, 1423, 1204, 1150, 1042, 829, 775, 756, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 3 H), 3.73 (s, 6 H), 4.34 (s, 2 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 6.31 (t, *J* = 2.4 Hz, 1 H), 6.36 (d, *J* = 2.3 Hz, 2 H), 7.35 (t, *J* = 9.7 Hz, 1 H), 7.48 (t, *J* = 9.9 Hz, 1 H), 7.74 (t, *J* = 9.8 Hz, 1 H), 8.23 (s, 1 H), 8.39 (d, *J* = 9.5 Hz, 1 H), 9.62 (d, *J* = 9.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 33.8, 55.3, 59.8, 97.9, 107.0, 115.7, 126.0, 127.4, 128.0, 135.2, 137.6, 139.0, 141.1, 141.2, 141.4, 143.6, 161.0, 165.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}O_4$: 351.1591; found: 351.1596.

1-[3-(Trifluoromethyl)phenyl]azulene (6a)

The organozinc reagent was prepared from 3-iodobenzotrifluoride according to TP2 with a concentration of 0.4498 M. According to TP3, a solution of **3c** (207 mg, 1 mmol) in THF was reacted with the organozinc reagent (2.4 mL, 0.4498 M) for 1 h to give, after purification by column chromatography (eluent: PE), **6a** as blue crystals; yield: 218 mg (80%); mp 67–68 °C.

IR (ATR, neat): 3059, 3028, 2959, 2924, 1574, 1447, 1393, 1342, 1303, 1269, 1165, 1107, 1069, 799, 779, 741, 702, 683, 648 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 9.9 Hz, 2 H), 7.49 (d, *J* = 4.0 Hz, 1 H), 7.62–7.68 (m, 3 H), 7.80–7.83 (m, 1 H), 7.91 (s, 1 H), 8.06 (d, *J* = 4.0 Hz, 1 H), 8.41 (d, *J* = 9.4 Hz, 1 H), 8.53 (d, *J* = 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.9, 122.6 (q, *J* = 272.2 Hz), 123.0 (q, *J* = 3.9 Hz), 123.8, 124.1, 126.4 (q, *J* = 3.7 Hz), 129.2, 129.7, 131.2 (q, *J* = 31.5 Hz), 133.0 (q, *J* = 1.5 Hz), 135.3, 135.6, 137.3, 137.8, 138.5, 138.6, 142.1.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{11}F_3$: 272.0813; found: 272.0804.

3-(Azulen-1-yl)benzonitrile (6b)

The organozinc reagent was prepared from 3-iodobenzonitrile according to TP2 with a concentration of 0.3958 M. According to TP3, a solution of **3c** (207 mg, 1 mmol) in THF was reacted with the organozinc reagent (2.8 mL, 0.3958 M) for 3 h to give, after purification by column chromatography (eluent: PE–Et_2O, 4:1, and CH_2Cl_2), **6b** as a blue oil; yield: 165 mg (72%).

IR (ATR, neat): 3059, 3028, 2226, 1589, 1574, 1477, 1393, 895, 796, 775, 736, 691, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.24 (m, 2 H), 7.44 (d, *J* = 4.0 Hz, 1 H), 7.54–7.62 (m, 2 H), 7.65 (t, *J* = 9.8 Hz, 1 H), 7.82 (td, *J* = 1.7, 7.5 Hz, 1 H), 7.87–7.88 (m, 1 H), 7.98 (d, *J* = 4.0 Hz, 1 H), 8.38 (d, *J* = 9.4 Hz, 1 H), 8.46 (d, *J* = 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.9, 118.0, 119.2, 124.0, 124.3, 128.5, 129.56, 129.61, 133.0, 134.0, 135.1, 135.6, 137.1, 137.9, 138.8, 138.9, 142.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{12}N$: 230.0964; found: 230.0956.

1-[3,5-Bis(trifluoromethyl)phenyl]azulene (6c)

The organozinc reagent was prepared from 1,3-bis(trifluoromethyl)-5-bromobenzene according to TP2 with a concentration of 0.5177 M. According to TP3, a solution of **3c** (207 mg, 1 mmol) in THF was reacted with the organozinc reagent (2.1 mL, 0.5177 M) for 5 h to give, after purification by column chromatography (eluent: PE–Et_2O, 5:1), **6c** as blue crystals; yield: 221 mg (65%); mp 67–68 °C.

IR (ATR, neat): 3055, 3028, 2916, 1396, 1362, 1312, 1273, 1169, 1119, 891, 845, 779, 741, 705, 682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dt, *J* = 3.7, 9.8 Hz, 2 H), 7.45 (d, *J* = 4.0 Hz, 1 H), 7.66 (t, *J* = 9.9 Hz, 1 H), 7.82 (s, 1 H), 8.01–8.02 (m, 3 H), 8.40 (d, *J* = 9.5 Hz, 1 H), 8.43 (d, *J* = 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.2, 119.8 (quint, *J* = 3.7 Hz), 123.7 (q, *J* = 272.9 Hz), 124.5, 124.8, 127.8, 129.5 (q, *J* = 3.7 Hz), 132.1 (q, *J* = 33.0 Hz), 134.9, 135.9, 137.3, 138.2, 139.0, 139.8, 142.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{11}F_6$: 341.0760; found: 341.0752.

Ethyl 4-(Azulen-2-yl)benzoate (7a)

The organozinc reagent was prepared from ethyl 4-iodobenzoate according to TP2 with a concentration of 0.4671 M. According to TP3, **3g** (104 mg, 0.5 mmol) was reacted with the organozinc reagent (1.17 mL, 0.4671 M) for 1 h to give, after column chromatography (eluent: CH_2Cl_2–PE, 4:1), **7a** as light-blue crystals; yield: 119 mg (86%); mp 204–206 °C.

IR (ATR, neat): 3051, 2974, 2932, 2905, 2870, 1709, 1574, 1462, 1408, 1362, 1269, 1180, 1092, 1015, 810, 772, 752, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 7.2 Hz, 3 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 7.18 (t, *J* = 9.8 Hz, 2 H), 7.55 (t, *J* = 9.8 Hz, 1 H), 7.71 (s, 2 H), 8.00 – 8.03 (m, 2 H), 8.12–8.15 (m, 2 H), 8.32 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 61.1, 115.0, 124.1, 127.5, 129.9, 130.3, 136.9, 137.4, 140.9, 141.5, 148.5, 166.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}O_2$: 277.1223; found: 277.1217.

4-(Azulen-2-yl)pyridine (7b)

The organozinc reagent was prepared as described for **4e** with a concentration of 0.3252 M. According to TP3, **3g** (104 mg, 0.5 mmol) was reacted with the organozinc reagent (1.69 mL, 0.3252 M) for 1 h. Then, the reaction mixture was quenched with H_2O (0.5 mL), diluted with CH_2Cl_2 (30 mL), and the organic layer was washed with sat. aq NH_4Cl–NH_3 (25% in H_2O) (1:1 mixture, 2 × 30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), evaporated, and the residue was purified using chromatography (eluent: Et_2O) to afford **7b** as blue crystals; yield: 78 mg (76%); mp 254–255 °C (Lit.[24] mp >200 °C).

IR (ATR, neat): 3051, 3032, 2924, 2851, 1532, 1574, 1547, 1462, 1447, 1408, 1211, 1018, 988, 953, 880, 799, 736, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 9.9 Hz, 2 H), 7.57–7.63 (m, 1 H), 7.72 (s, 2 H), 7.80 (dd, *J* = 1.7, 4.6 Hz, 2 H), 8.36 (dd, *J* = 1.0, 10.0 Hz, 2 H), 8.69 (dd, *J* = 1.7, 4.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.0, 122.0, 124.3, 137.8, 138.2, 141.4, 143.9, 146.4, 150.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N$: 206.0964; found: 206.0961.

2-[3-(Trifluoromethyl)phenyl]azulene (7c)

The organozinc reagent was prepared from 3-iodobenzotrifluoride according to TP2 with a concentration of 0.5361 M. According to TP3, **3g** (104 mg, 0.5 mmol) was reacted with the organozinc reagent (1.0 mL, 0.5361 M) for 30 min to give, after purification by column chromatography (eluent: CH_2Cl_2–PE, 4:1), **7c** as blue crystals; yield: 116 mg (85%); mp 160–161 °C.

IR (ATR, neat): 3059, 3024, 2955, 2924, 1408, 1342, 1315, 1169, 1111, 1076, 802, 740, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 9.9 Hz, 2 H), 7.54–7.62 (m, 3 H), 7.69 (s, 2 H), 8.11–8.13 (m, 1 H), 8.20 (s, 1 H), 8.32–8.35 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.6, 124.2, 124.4 (q, *J* = 4.0 Hz), 124.7 (q, *J* = 3.7 Hz), 125.0 (q, *J* = 272.2 Hz), 129.5, 130.8 (q, *J* = 1.5 Hz), 131.4 (q, *J* = 32.3 Hz), 136.9, 137.4, 137.5, 141.5, 148.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{12}F_3$: 273.0886; found: 273.0880.

1,3-Diphenylazulene (8a)

The organozinc reagent was prepared from iodobenzene according to TP2 with a concentration of 0.4694 M. According to TP3, **3d** (286 mg, 1 mmol) was reacted with the organozinc reagent (4.6 mL, 0.4694 M) for 30 min to give, after purification by column chromatography (eluent: PE), **8a** as green crystals; yield: 198 mg (71%); mp 104–105 °C (Lit.[25] mp 100–102 °C; Lit.[14a] mp 114–116 °C).

IR (ATR, neat): 3051, 3036, 2955, 2924, 2855, 1593, 1566, 1481, 1427, 1366, 876, 760, 737, 702, 640, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 10.0 Hz, 2 H), 7.40–7.44 (m, 2 H), 7.54–7.63 (m, 5 H), 7.69–7.71 (m, 4 H), 8.18 (s, 1 H), 8.60 (d, *J* = 9.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.6, 126.6, 128.8, 130.0, 130.7, 136.3, 136.8, 137.3, 137.4, 139.1.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{22}H_{16}$: 280.1252; found: 280.1242.

Diethyl 4,4′-(Azulene-1,3-diyl)dibenzoate (8b)

The organozinc reagent was prepared from ethyl 4-iodobenzoate according to TP2 with a concentration of 0.3731 M. According to TP3, **3d** (286 mg, 1 mmol) was reacted with the organozinc reagent (5.6 mL, 0.3731 M) for 30 min to give, after purification by column chromatography (eluent: CH_2Cl_2–PE, 4:1 and PE–Et_2O, 2:1), **8b** as green crystals; yield: 411 mg (97%); mp 127–128 °C.

IR (ATR, neat): 3044, 2978, 2936, 2866, 1705, 1601, 1427, 1358, 1261, 1227, 1177, 1015, 860, 772, 741, 710, 575 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 6 H), 4.44 (q, *J* = 7.2 Hz, 4 H), 7.22 (t, *J* = 10.0 Hz, 2 H), 7.66 (t, *J* = 9.8 Hz, 1 H), 7.72–7.63 (m, 4 H), 8.16 (s, 1 H), 8.20–8.16 (m, 4 H), 8.57 (d, *J* = 9.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 61.1, 124.9, 128.5, 129.6, 129.8, 130.1, 136.5, 137.4, 137.6, 139.7, 141.6, 166.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{25}O_4$: 425.1748; found: 425.1741.

1,3-Bis[3-(trifluoromethyl)phenyl]azulene (8c)

The organozinc reagent was prepared from 3-iodobenzotrifluoride according to TP2 with a concentration of 0.5088 M. According to TP3, **3d** (286 mg, 1 mmol) was reacted with the organozinc reagent (4.3 mL, 0.5088 M) for 1 h to give, after purification using column chromatography (eluent: PE), **8c** as a cyan solid; yield: 260 mg (62%); mp 138–139 °C.

IR (ATR, neat): 3075, 3051, 2959, 2920, 2874, 1574, 1454, 1319, 1265, 1153, 1111, 1067, 880, 795, 737, 698, 570 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 10.2 Hz, 2 H), 7.62–7.71 (m, 5 H), 7.81–7.84 (m, 2 H), 7.90–7.91 (m, 2 H), 8.14 (s, 1 H), 8.53 (d, *J* = 9.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.4 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 272.2 Hz), 124.8, 126.6 (q, *J* = 3.7 Hz), 129.2, 129.3, 131.4 (q, *J* = 32.3 Hz), 133.1 (q, *J* = 1.5 Hz), 136.3, 137.23, 137.26, 137.9, 139.7.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{24}H_{14}F_6$: 416.1000; found: 416.0986.

Ethyl 4-[3-(Pyridin-4-yl)azulen-1-yl]benzoate (8d)

The first organozinc reagent was prepared from ethyl 4-iodobenzoate according to TP2 with a concentration of 0.4671 M. The second organozinc reagent was prepared from 4-iodopyridine as described for **4e** with a concentration of 0.3252 M. According to TP3, **3d** (286 mg, 1 mmol) was reacted with the first organozinc reagent (2.14 mL, 0.4671 M) for 1 h. Then the second zinc reagent (3.1 mL, 0.3252 M) was added and reaction mixture was stirred overnight. The mixture was quenched with H_2O (0.5 mL), diluted with CH_2Cl_2 (30 mL), and the organic layer was washed with sat. aq NH_4Cl–NH_3 (25% in H_2O) (1:1 mixture, 2 × 30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$), evaporated, and the residue was purified using column chromatography (eluent: CH_2Cl_2–Et_2O, 2:1) to afford **8d** as a green solid; yield: 150 mg (42%); mp 178–179 °C.

IR (ATR, neat): 3024, 2978, 2924, 2855, 1709, 1593, 1427, 1362, 1269, 1176, 1099, 864, 837, 772, 710, 574 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.2 Hz, 3 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 7.27 (dt, *J* = 4.0, 9.7 Hz, 2 H), 7.54–7.56 (m, 2 H), 7.67–7.72 (m, 3 H), 8.15 (s, 1 H), 8.16–8.20 (m, 2 H), 8.60 (t, *J* = 9.0 Hz, 2H), 8.70 (d, *J* = 4.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 61.1, 124.4, 125.3, 127.5, 128.7, 129.6, 130.07, 130.14, 136.1, 136.7, 137.2, 137.6, 138.0, 139.9, 141.4, 144.7, 150.1, 166.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}NO_2$: 354.1489; found: 354.1486.

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Supporting Information

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