Azulene Functionalization by Iron-Mediated Addition to a Cyclohexadiene Scaffold

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ABSTRACT: The functionalization of azulenes via reaction with cationic \( \eta^5 \)-iron carbonyl diene complexes under mild reaction conditions is demonstrated. A range of azulenes, including derivatives of naturally occurring guaiazulene, were investigated in reactions with three electrophilic iron complexes of varying electronic properties, affording the desired coupling products in 43−98% yield. The products were examined with UV−vis/fluorescence spectroscopy and showed interesting halochromic properties. Decomplexation and further derivatization of the products provide access to several different classes of 1-substituted azulenes, including a conjugated ketone and a fused tetracycle.

INTRODUCTION

Azulene is a bicyclic nonalternant aromatic hydrocarbon, isomeric with naphthalene. The \( \pi \)-electrons of azulene are polarized toward the five-membered ring, resulting in a relatively large inherent dipole moment and a deep blue color.\(^1\) Their unusual electronic properties make azulenes interesting as photocatalysts\(^2\) and colorimetric indicators\(^3\) and for optoelectronics such as solar cells,\(^4\) photoswitches,\(^5\) and organic electronics.\(^6\) Azulene derivatives have also found use in medicine in the form of antiulcer,\(^7\) antidiabetic,\(^8\) and anticancer\(^9\) agents. The ability to functionalize the azulene scaffold is thus of great interest.

Azulenes are potent nucleophiles for electrophilic aromatic substitution (SEAr), with the 1- and 3-positions being the most reactive toward electrophiles.\(^10\) Reported methods for derivatizing azulenes include (a) the Michael addition,\(^11\) (b) Friedel−Crafts\(^11a,12\) and Vilsmeier−Haack reactions,\(^11a,13\) (c) azulene addition to heteroaromatic triflates,\(^14\) and (d) the formation of diazo compounds (Scheme 1).\(^15\) Azulenes are also susceptible to (e) electrophilic halogenations.\(^10c,16\) In addition, cross-coupling reactions have been reported.\(^17\) While these latter reactions are attractive for coupling the azulene to sp\(^2\) and sp-carbons, they generally rely on the use of precious metal catalysts and require prefunctionalization of the azulene scaffold.

Another class of electrophile that could potentially react with nucleophilic azulenes are cationic \( \eta^5 \)-iron carbonyl dienyl complexes (Scheme 2). Such complexes are capable of reacting with a wide range of nucleophiles to form new carbon−carbon or carbon−heteroatom bonds.\(^18\) Nucleophilic addition proceeds in a highly selective manner at the opposite face to the iron carbonyl moiety and at one of the ends of the conjugated system.\(^18b,19\) Substituents on the cation can act to direct the nucleophilic addition to either termini of the dienyl system;

Scheme 1. Electrophilic Aromatic Substitution Reactions for Functionalizing Azulenes

Scheme 2. Methods for the Formation of Cationic Iron Carbonyl Dienyl Complexes

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electron-withdrawing groups will generally favor addition in the meta position, while electron-donating groups will often favor the para or ipso addition. The cationic complexes can be formed via hydride abstraction (Scheme 2, path a) or by acid treatment of a complex possessing a leaving group (Scheme 2, path b). Once formed, the complex can be isolated as a shelf-stable fine powder.22

Aromatic nucleophiles that can react with cationic iron carbonyl dienyl complexes include furan,21 indole,21,22 aniline,23 and oxygenated arenes. The scope was recently increased by us to include the selective C- or O-addition of phenolic nucleophiles.25 Although azulenes, with a nucleophilicity similar to that of indoles,10d can be expected to be efficient nucleophiles, no previous report of their use in this context has been reported. Herein, we present a convenient iron-mediated electrophilic C–H functionalization of azulenes (Scheme 1). The products of this process are valuable in two contexts. First, they are stimuli-responsive substances with multimodal outputs (colorimetric, fluorescence, and infrared spectroscopic). Second, they are versatile substrates for further synthetic transformations such as cyclizations. The cyclohexadiene also constitutes a proaromatic substituent, which may be readily converted to a phenyl ring, giving a formal product of azulene electrophilic arylation, for which there is no direct S$_2$Ar equivalent.

**RESULTS AND DISCUSSION**

To investigate if azulenes could react with cationic iron carbonyl dienyl complexes, we selected guaiazulene 1 as the nucleophile, due to its low cost and availability from natural sources. As the electrophile, we selected iron complex 2, which we have used in earlier studies.25 Optimization of the reaction conditions for this addition was then performed (Table 1).

| entry | solvent | base | yield (%), 3 |
|-------|---------|------|-------------|
| 1     | EtOH    |      | 41          |
| 2     | H$_2$O  |      | 72          |
| 3     | acetone/H$_2$O (3:1) | Et$_3$N | 85          |
| 4     | MeOAc   | Et$_3$N | 75          |
| 5     | acetone | Et$_3$N | 73          |
| 6     | acetone | NaHCO$_3$ | 97          |

*Products are racemic with the relative stereochemistry shown. *Yields are determined by quantitative $^1$H NMR using p-xylene as the internal standard.

In our previous studies involving phenolic nucleophiles, we performed the reaction in ethanol in the absence of base at an ambient temperature.25 Similar conditions here afforded the desired addition product 3, albeit in a modest yield (Table 1, entry 1). Using water as the solvent afforded a heterogeneous reaction mixture where both guaiazulene and iron complex 2 were insoluble. Nevertheless, the yield was increased to 72% (entry 2). To investigate if solubility issues might play a role in limiting the yield, the reaction was performed in a 3:1 mixture of acetone and water, resulting in an enhanced yield of 85% (entry 3). Adding an amine base such as triethylamine (Et$_3$N) was not beneficial, neither for methyl acetate as the solvent (entry 4) nor for acetone (entry 5). A near-quantitative yield could, however, be attained using acetone with sodium bicarbonate as the base (entry 6). This last protocol thus provides a set of green and benign reaction conditions for the addition reaction.

Azulene itself possesses two nucleophilic carbons, and a mixture of mono- and disubstituted products is thus to be expected. To see if azulene could be selectively functionalized to form either one of these products, the reaction was first performed using a slight excess of complex 2 relative to azulene. This afforded an equimolar mixture of the diastereomeric disubstituted azulenes 4 and 4' in an 81% yield (Scheme 3). Using a large excess of azulene instead, a mixture of mono- and disubstituted products was formed, where the monosubstituted product 5 could be isolated in a yield of 48%.

The scope of the transformation was then explored further. In addition to the activated complex (2), electronically neutral 6 and deactivated complex 7 were also selected for evaluation as electrophiles in the reaction (Figure 1).

Azulenes with extended π-systems are of interest for optoelectronic applications, as the properties of azulene can be tuned by extension of the conjugated system.4c Routes to

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**Scheme 3. Mono- and Dialkylation of Azulene**

**Table 1. Optimization of the Addition of Guaiazulene (1) to Cationic Complex 2**

**Figure 1. Cationic iron carbonyl dienyl complexes 2, 6, and 7, selected as electrophilic coupling partners.**
functionalizing these types of motifs could thus be valuable. A selection of 1-substituted azulene nucleophiles (8–11, Figure 2), as well as a 6-substituted azulene (12), was prepared and explored in reactions with iron complexes 6 and 7.

Figure 2. Scope of azulene nucleophiles with extended π-systems.

Azulene is significantly more expensive than guaiazulene. As nucleophiles 8–11 were prepared from azulene itself, they were used as the limiting reagent in the ensuing reactions. The results of their reaction with electrophiles 6 or 7 are shown in Scheme 4. Treating 1-phenylazulene 8 with 1.1 equiv of iron complex 6 resulted in the formation of 13 in an excellent yield of 95%. The less activated iron complex 7 was equally effective with the same nucleophile, resulting in 94% of adduct 14. Azulene 9, with a thiienyl functionality, reacted with 6 to form compound 15 in a 73% yield. No other coupling products were detected, indicating that the thiophene unit does not compete with azulene as a nucleophile in this case. Azulene 10, with a pendant alkyne group, and formylated azulene 11 afforded adducts 16 and 17 in 70 and 50% yields, respectively. These products contain functional handles, which can be utilized for further derivatization. As in the case of azulene, 6-phenylazulene 12 possesses two nucleophilic sites and could be doubly alkylated using an excess of the cationic iron complex 6, giving rise to an equimolar mixture of diastereomers 18 and 18′ in an 83% yield.

Naturally occurring guaiazulene (1) is an FDA-approved additive in cosmetics. Being a large-scale commercial product, it is inexpensive and readily available and therefore of special interest for synthetic applications. In addition to guaiazulene itself, seven guaiazulene derivatives (19–25) with different substitution patterns on the five-membered ring were prepared to be used as nucleophiles in the addition reaction. Substituents included both electron-withdrawing and electron-donating groups, along with some potentially useful synthetic handles in the form of a boronic ester or a halogen (Figure 3).

Addition of the guaiazulene nucleophiles 1 and 19–25 was performed using the optimized conditions shown in Table 1. The results are summarized in Scheme 5. Addition of guaiazulene itself to electrophilic iron complex 2 proceeded to give addition product 3 in an excellent yield of 97%. Complexes 6 and 7 were less reactive, but upon extending the reaction time from 4 to 16 h, alkylated azulenes 26 and 27 were obtained in yields of 98% and 93%, respectively. A deactivating effect was seen for the more electron-deficient 1-formyl-substituted guaiazulene derivative 19, where compound 28 was produced in a 56% yield. The coupling reaction proved to be sensitive toward substituents in the 2-position of the guaiazulene scaffold. Guaiazulene derivative 20, with a boronic ester in the 2-position, reacted with iron complex 2 to produce 29 in a 43% yield. 2-Iodogaiazulene (21) reacted sluggishly, but a 63% yield of 30 could be attained using a reaction time of 16 h and an excess of cation 2. The bromo-substituted guaiazulene 22 showed a higher reactivity, resulting in 79% of product 31 under the standard reaction conditions, with a 4 h reaction time. This suggests that steric factors may influence the reaction outcome in the case of 2-substituted azulenes. No reaction occurred with the tolyl-substituted derivative 23. For the coupling with 2-aminogaiazulene (24), competing N-addition is a possibility. The reaction was unsuccessful, however; while all starting material was consumed, neither C- or N-addition product could be isolated. To investigate if this reaction outcome was linked to instability introduced by the amino group, compound 24 was acetylated to amide 25 and the latter was subsequently used in a coupling reaction. While 1H NMR analysis of the crude product looked promising, no product could be isolated in this case.

Scheme 4. Alkylation of Azulene Nucleophiles 8−12

| 8-12 | 6-7 | R | NaHCO₃ (2 equiv) |
|------|-----|----|-----------------|
| 8-12 | 6-7 | R | acetone rt, 5h   |

13 95% 14 94%

15 73% 16 70% 17 50%

18 18′ 83% 18′

**a** Products are racemic with the relative stereochemistry shown. **b** Isolated yields. **c** 16 h reaction time. **d** 2.2 equiv electrophile, 4 equiv NaHCO₃.
In our previous research on phenolic nucleophiles, we developed a shorter route for the coupling reaction starting from neutral iron cyclohexadiene complexes. This method foregoes the formation and isolation of the cationic iron carbonyl complex by forming the electrophile in situ from a neutral precursor using a catalytic amount of acid. We applied this strategy here and found that guaiazulene could be alkylated directly from the neutral iron complex (precursor to cationic complex) in the presence of tetrafluoroboric acid (Scheme 6). When a catalytic amount of acid was used, only a small amount of product was formed. Upon increasing the amount of tetrafluoroboric acid to 1.1 equiv, however, the desired addition product was obtained in an 86% yield. Using an excess of acid (2 equiv) lowered the yield to 45%, which may be due to protonation of guaiazulene, reducing its nucleophilicity. The 86% yield obtained under the optimal conditions is higher than the combined 76% yield obtained when preforming the complex, followed by the addition of guaiazulene, opening up for a shorter synthetic path. As the isolation of the cationic complex includes precipitation using large amounts of solvent, this variant of the reaction can significantly reduce the amount of waste created in the synthesis of products such as 3.

Iron carbonyl complexes are of interest as bioprobes, indicating that the azulenes formed in this study could be useful in their own right. In addition to a strong and distinctive absorption in the IR region from the iron carbonyl moiety, the azulene fragment introduces both a fluorophore and a clearly visible colorimetric indicator, thus potentially allowing multimodal chemical sensing. Accordingly, we investigated the UV−vis, fluorescence, and IR spectroscopic properties of a representative selection of the novel compounds reported here.

Azulene derivatives are known sometimes to exhibit halochromism, i.e., to undergo changes in color upon protonation (at the azulene-1- or 3-position). Compounds 4/4′, 14, 26, 33, and 34 were assessed for their colorimetric responses to trifluoroacetic acid (TFA). Exposure to excess TFA (1000 equiv) resulted in each case in a color change discernible to the naked eye (Figure S67, see the Supporting Information (SI)), which became more pronounced when TFA was used as cosolvent (Figure 4). UV−vis absorption spectra of the neutral and protonated azulenes were also acquired (Figure S68). The relationship between azulene substitution pattern and halochromism has been studied and a trend can be determined. It has been shown that for some strongly halochromic azulenes with a particular substituent at the 2- or 6-position, moving the substituent to the 1- or 3-position may significantly attenuate the halochromic response. This may be due to the change in connectivity resulting in a different preferred site of protonation. The tricarbonyliron(diene)-substituted azulenes 4/4′, 14, and 26 exhibit pronounced halochromism regardless of the fact the substituents are at 1- and 3-positions of the azulene core. This suggests that in 4/4′, 14, and 26, the azulene core remains the
preferred site of protonation, as opposed to the tricarbonyliron(diene) motif. It is known that for many azulenes, protonation can induce a significant fluorescence turn-on response, whereas fluorescence properties of tricarbonyliron(diene) complexes have been studied only rarely. Exposure to UV irradiation is an established method of cleaving Fe–C bonds in tricarbonyliron(diene) complexes (see below), but the reaction time required for this process is >3 orders of magnitude greater than the acquisition time for a fluorescence spectrum (days vs seconds). On the basis of this semiquantitative consideration, we reasoned that fluorescence spectra could nevertheless be acquired. Compounds 4/4’, 14, 26, 33, and 34 were all found to exhibit significant fluorescence enhancement upon addition of TFA, with 4/4’ showing the greatest turn-on response (λex = 266 nm, λem = 336 nm; Figure 5), and our current findings show that the tricarbonyliron(diene) motif does not quench the fluorescence of the pendent azulenium fluorophore. A titration of azulene 4/4’ with TFA was also performed, monitored by UV−vis and fluorescence spectroscopy (Figures S69 and S70). A weak second emission maximum was observed at higher acid concentrations, implying a possible further reaction under these conditions.

Iron carbonyl diene complexes exhibit strong vibrational absorption bands in the 2100−1800 cm−1 region, a window where most biological media are transparent. This makes them interesting in applications such as bioimaging using mid-IR and Raman spectroscopy. Iron carbonyl diene complexes substituted with fluorescent coumarin moieties have been suggested as IR-fluorescent probes, and we therefore envision that the azulene-functionalized iron carbonyl complexes could be useful for similar applications. The IR-absorption spectra of the azulene addition products were measured using attenuated total reflection (ATR)-Fourier transform infrared (FTIR) in the neat state. As expected, characteristic strong peaks in the 2100−1900 cm−1 region were observed for all products possessing the iron carbonyl moiety. To increase the synthetic utility of the formed products, we investigated the oxidative removal of the iron carbonyl moiety. Several methods have been developed for this transformation, where strong oxidative conditions are generally used, including the use of hydrogen peroxide in aqueous sodium hydroxide, cerium ammonium nitrate, trimethylamine N-oxide, or cupric chloride. Initial application of these methods, however, showed that these conditions were too harsh for these compounds, resulting in poor yields, partial degradation of the oxidatively sensitive azulenes, and in some cases partial aromatization of the formed cyclohexadiene. Successful demetallation of the addition products could, however, be achieved by applying mild, photolytic decomplexation conditions, using a modification of a procedure reported by Knöllker. Irradiation of an acetonitrile solution of 13 with a low-energy UV light (370 nm, 15 W) for 72 h, in the presence of air, yielded the free diene 33 in a 78% yield (Scheme 7, entry 1). An advantage of the current procedure is that the demetallation can be carried out without the need for specialized equipment. However, it is likely that the reaction time can be significantly shortened with a more powerful light source. Notably, this photolytic decomplexation is more tolerant toward oxidatively labile groups than traditional...
methods. The free diene could also be liberated without concomitant aromatization. This has previously proved to be difficult for iron complexes possessing an aromatic substituent, which is not conjugated to the diene. Photolytic demetallation of the methoxy-substituted adduct 14 instead resulted in the formation of unsaturated ketone 34 in a 74% yield (Scheme 7, entry 2). This type of reactivity is known upon decomplexation of 2-methoxy-substituted iron carbonyl cyclohexadiene complexes and provides access to a different compound class in terms of substituted azulenes. Guaiazulene-derived adduct 27 could also be demetallated (Scheme 7, entry 3), affording the unsaturated ketone 35 in a 42% yield.

Another product class could be accessed by oxidative aromatization of diene 33 using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), producing 1,3-diphenylazulene (36) in an 82% yield (Scheme 8).

Scheme 8. Aromatization of Free Diene

The C-4 methyl group of guaiazulene is acidic. Upon deprotonation, the formed anion is stabilized via conjugation with the electron-poor seven-membered ring. This has been utilized for condensation reactions with aldehydes under basic conditions. Limited examples of conjugate additions have also been reported in this context. Demetallated guaiazulene derivative 35 possesses an unsaturated ketone moiety in close proximity to the C-4 methyl group, which could allow for an intramolecular conjugate addition. We were pleased to see that the treatment of 35 with t-BuOK in tetrahydrofuran (THF) at 0 °C yielded a tetracyclic product 37 in a 39% yield (Scheme 9). A strong nuclear Overhauser effect (NOE) interaction between the two ring-junction protons indicates a cis-fused ring system. The formed tetracyclic compound possesses an unusual 6/6/5/7 ring system, similar to the carbon skeleton of swinhoeisterols, isolated from the marine sponge Theonella swinhoei. Swinhoeisterols have been reported to have cytotoxic properties and have recently been the target of a total synthesis. We therefore envision that tetracyclic structures of this type could be of interest in the synthesis of natural products and bioactive compounds. A photoswitch incorporating guaiazulene and cyclohexene was recently reported by Hecht and co-workers, and compounds such as 35 and 37 may find additional applications in this area.

Scheme 9. Base-Mediated Cyclization of Demetallated Guaiazulene Derivative 35 Forming Tetracycle 37

**CONCLUSIONS**

Azulenes are here shown to be competent nucleophiles in the addition to cationic iron carbonyl dienyl complexes with different electronic properties. The reaction proceeds smoothly at room temperature with acetone as the solvent, using an inexpensive base (NaHCO₃) as the only additive. Apart from azulene itself, functionalized azulenes with extended conjugated systems, as well as derivatives of naturally occurring guaiazulene, were evaluated as nucleophiles affording the targeted products in a 43–98% yield. Photolytic decomplexation allowed the oxidative removal of iron under mild conditions. The synthetic utility of the formed azulenes was demonstrated via further transformations, including the formation of a tetracyclic product. UV−vis and fluorescence properties of selected products were also explored, displaying some unusual halochromic properties. In conclusion, we believe that the reported methodology provides a valuable new method for azulene derivatization and could find applications in areas such as optoelectronics, sensors, pharmaceuticals, and natural product synthesis.
General Considerations. 1-(Azulen-1-yl)tritylhydroquinone hexafluorophosphate, H2O), neutral iron carbonyl complex 32, cationic iron carbonyl complexes 2, 6, 43 and 44 (starting from commercial 1-methoxy-1,3-cyclohexadiene, technical grade 65%), and guaiazulene derivatives 11, 45, 12, 46, 19, 20, 22, 27 and 37 were synthesized according to literature procedures. All other solvents and reagents were purchased from commercial suppliers and used without purification or drying, unless otherwise stated. Photocatalytic decomplexation was performed using a low-energy black light lamp (Velleman lighting, 15 W, 850 lm). Structural assignments were made with additional information from gradient correlation spectroscopy (gCOSY), gradient heteronuclear single-quantum coherence (gHSQC), nuclear Overhauser enhancement spectroscopy (NOESY), and gradient heteronuclear multiple-bond correlation (gHMBC) experiments.

Analytical Methods. Column chromatography was performed on a Biotage Isola Spectra One with Biotage SNAP KP-sil (silica gel) or KP-C18-HS (C18, reverse phase) columns. NMR spectra, 1H NMR and 13C NMR, were recorded on an Agilent 400 MHz (101 MHz) spectrometer with tetramethylsilane as the residual solvent peak for reference. The following abbreviations are used for reporting NMR peaks: singlet (s), doublet (d), triplet (t), quartet (q), heptet (hept), multiplet (m), broad (br), and apparent (app). All coupling constants (J) are reported in hertz (Hz). For diastereomeric mixtures, peaks that can be attributed to single diastereomers are labeled d1/d2, d3/d4, ATR-FTIR spectra were recorded on a PerkinElmer Spectrum infrared spectrometer with a pike-GladiATR module and reported in wavenumber (cm−1). Melting points were recorded on a Buchi Melting Point B-545. High-resolution mass spectrometry (HRMS) was performed on an Agilent 1290 Infinity LC system equipped with an autosampler tandem to an Agilent 6520 Accurate Mass Q-TOF LC/MS.29a Fluorescence spectra were acquired on an Agilent Technologies Cary Eclipse fluorescence spectrophotometer. UV–vis spectra were acquired on a PerkinElmer Lambda20 Spectrophotometer, using a Starna Silica (quartz) cuvette with 10 mm path length, two faces polished.

General Procedure A: Addition of Guaiazulene-Derived Nucleophiles to Cationic Iron Carbonyl Complexes. Cationic iron carbonyl complex (1.0 equiv), guaiazulene derivative (1.1 equiv), NaHCO3 (2.0 equiv), and acetone (1.0 mL) were added to a 5 mL microwave vial equipped with a stir bar. The vial was capped, and stirred at room temperature for 24 h. The reaction mixture was diluted with diethyl ether, filtered through a pad of basic aluminum oxide, and the solvent was evaporated under a stream of N2 gas. Purification by flash column chromatography yielded 3 as a blue solid (41.7 mg, 86%). mp 46–47 °C; [H NMR (400 MHz, chloroform-d) δ 8.02 (d, J = 2.2 Hz, 1H), 7.46 (s, 1H), 7.24 (dd, J = 10.6, 2.2 Hz, 1H), 6.31 (dd, J = 4.4, 0.8 Hz, 1H), 5.56 (dd, J = 6.4, 4.4 Hz, 1H), 4.56 (app dt, J = 11.3, 3.9 Hz, 1H), 3.73 (s, 3H), 3.44 (dd, J = 6.5, 3.3, 1.4 Hz, 1H), 3.00 (hept, J = 6.9 Hz, 1H), 2.96 (s, 3H), 2.87 (dd, J = 15.2, 11.3 Hz, 1H), 2.59 (s, 3H), 1.60 (ddd, J = 15.2, 4.3, 0.9 Hz, 1H), 1.32 (d, J = 6.9 Hz, 6H); 195.1199. 13C NMR (101 MHz, chloroform-d) δ 172.6, 144.5, 139.7, 138.5, 136.4, 134.5, 133.7, 131.9, 129.6, 124.9, 88.7, 84.7, 69.1, 62.8, 51.6, 39.4, 37.6, 33.7, 27.4, 24.5, 13.1. Signal for Fe–CO not seen; FTIR-ATR fmax/cm−1 2047 (Fe–CO), 1755 (Fe–CO), 1705 (C=O); HRMS (ESI+)/mz: [M + H]+ calcd for C32H25FeO10 681.0147; found 681.0139.

Tricarbonyl[dimethyl 5′-(azulen-1-yl)cyclohexa-1,3-diene-1-carboxylato]iron (5). Synthesized according to general procedure B using azulene (12.9 mg, 0.101 mmol), iron complex 2 (93.4 mg, 0.221 mmol), and NaHCO3 (33.8 mg, 0.403 mmol). The product was purified by reversed-phase flash chromatography (MeOH/H2O 85:15), yielding an equimolar mixture of diastereomers 4a and 4b as a blue-green amorphous solid (55.1 mg, 81%). [H NMR (400 MHz, chloroform-d) δ 8.14 and 8.13 (d, d, J = 7.5 Hz, 2H), 7.50 (app t, J = 9.8 Hz, 1H), 7.41 and 7.38 (d, d, J = 3.9 Hz, 2H), 7.02 and 7.02 (d, d, J = 8.6, 4.4 Hz, 2H); 1H NMR (101 MHz, chloroform-d) δ 172.6, 144.5, 139.7, 138.4, 138.4, 135.6, 133.5, 133.5, 133.2, 133.1, 131.4, 131.4, 129.1, 121.8, 89.2, 89.2, 84.5, 67.6, 67.4, 63.0, 62.9, 51.9, 37.2, 37.1, 32.8, 32.6; FTIR-ATR fmax/cm−1 2048 (Fe–CO), 1967 (Fe–CO), 1703 (C=O); HRMS (ESI+)/mz: [M + H]+ calcd for C26H27FeO5 475.1208; found 475.1199.

1-Phenylazulene (8). 1-Phenylazulene was synthesized according to a literature procedure.79d A to a Radleys Carousel reaction tube equipped with a stirrer was added 1-(azulenyl-1-yl)tritylhydroquinone hexafluorophosphate (500 mg, 1.39 mmol), phenylboronic acid (203 mg, 1.67 mmol), iron complex 2 (42.2 mg, 0.100 mmol), phenylboronic acid (203 mg, 1.67 mmol), and Pd(OAc)2 (12.5 mg, 0.0557 mmol). The vial was capped, and the crude product was purified by flash column chromatography (100% petroleum ether), yielding 8 as a blue solid (166.7 mg, 59%). [H NMR (400 MHz, chloroform-d) δ 8.57 (d, J = 9.8 Hz, 1H), 8.36 (d, J = 9.4 Hz, 1H), 8.03 (d, J = 3.8 Hz, 1H), 7.65–7.57 (m, 3H), 7.53–7.48 (m, 2H), 7.45 (d, J = 3.9 Hz, 1H), 7.38–
Synthesized according to a literature procedure. To a Radleys Carousel reduced volume reaction tube equipped with a stirrer was added 1-(azulen-1-yl) tetrahydrothiophenium hexafluorophosphate (250 mg, 0.694 mmol), 2-(thiophen-2-yl)pinacol ester (175 mg, 0.833 mmol), K2PO3 (295 mg, 1.39 mmol), Xphos (33 mg, 0.0694 mmol), and Pd(OAc)2 (6.2 mg, 0.028 mmol). The vial was capped, evacuated, and refilled with argon. DMP (5.0 mL) was added, and the vial was heated in a heating block at 75 °C for 6 h. The crude product was diluted with water and extracted with petroleum ether, and the organic phase was washed with brine and 5% aqueous lithium chloride. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography (100% petroleum ether), yielding 9 as a blue-green oil (77.5 mg, 53%).1H NMR (400 MHz, chloroform-d) δ 8.77 (d, J = 9.8 Hz, 1H), 8.32 (d, J = 9.4 Hz, 1H), 8.07 (d, J = 4.0 Hz, 1H), 7.64–7.67 (m, 1H), 7.41 (d, J = 4.0 Hz, 1H), 7.38–7.35 (m, 1H), 7.32–7.31 (m, 1H), 7.23–7.15 (m, 13H); 13C{1H} NMR (101 MHz, chloroform-d) δ 142.3, 139.0, 138.7, 137.5, 137.4, 135.9, 135.1, 127.8, 124.7, 124.5, 123.8, 123.7, 117.9. Analysis data are in accordance with published data for this compound.

(Azulen-1-ylthio)trisopropylsilane (10). To a microwave reaction vial was added 1-(azulen-1-yl) tetrahydrothiophenium hexafluorophosphate (100 mg, 0.278 mmol), Cul (5.3 mg, 0.028 mmol), K2PO3 (64.8 mg, 0.305 mmol), Bu3P (11.8 mg, 0.027 mmol), and Pd(OAc)2 (3.1 mg, 0.014 mmol). The vial was capped, evacuated, and refilled with argon. (Triisopropylsilyl)acetophenone (94 μL, 0.419 mmol) and 2.0 mL DME were added, and the vial was heated in a heating block at 80 °C for 16 h. The crude product was diluted with water and extracted with petroleum ether. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography (100% petroleum ether), yielding 10 as a yellow oil (23.7 mg, 27%).1H NMR (400 MHz, chloroform-d) δ 8.59 (d, J = 9.6 Hz, 1H), 8.28 (d, J = 9.4 Hz, 1H), 7.98 (d, J = 4.0 Hz, 1H), 7.63 (app t, J = 9.9 Hz, 1H), 7.30–7.18 (m, 3H), 1.22–1.19 (m, 21H); 13C{1H} NMR (101 MHz, chloroform-d) δ 142.0, 141.3, 140.0, 138.7, 137.3, 136.5, 124.7, 124.2, 117.5, 111.4, 103.3, 94.8, 19.0, 11.7; FTIR-ATR v max/cm−1 2133 (C=C); HRMS (ESI+) m/z: [M + H]+ calc f= C25H19FeO3S 429.0246; found 429.0246.

Tricarbonyl[1-(cyclohexa-2,4-dien-1-yl)]azulene-1-carbaldheyde (17). Synthesized according to general procedure B using azulene derivative 8 (20.6 mg, 0.101 mmol), iron complex 6 (40.5 mg, 0.111 mmol), and NaHCO3 (8.4 mg, 0.10 mmol) in 0.5 mL acetonitrile. The product was purified by flash chromatography (petroleum ether/EtOAc 99:1), yielding 17 as a sticky green solid (15.6 mg, 73%).1H NMR (400 MHz, chloroform-d) δ 8.61 (d, J = 9.6 Hz, 1H), 8.18 (d, J = 9.6 Hz, 1H), 7.86 (s, 1H), 7.53 (app t, J = 9.8 Hz, 1H), 7.36 (dd, J = 5.1, 1.2 Hz, 1H), 7.25 (dd, J = 3.6, 1.2 Hz, 1H), 7.18 (dd, J = 5.1, 3.5 Hz, 1H), 7.07 (app t, J = 9.8 Hz, 1H), 7.06 (app t, J = 9.8 Hz, 1H), 5.63–5.58 (m, 1H), 5.48 (dd, J = 6.0, 1.5 Hz, 1H), 4.02 (app dt, J = 11.1, 1.6 Hz, 2H), 3.45–3.32 (m, 2H), 2.56 (dd, J = 15.1, 1.1, 3.8 Hz, 1H), 1.83 (dd, J = 15.2, 3.2, 1.1 Hz); 13C{1H} NMR (101 MHz, chloroform-d) δ 190.0, 139.0, 138.5, 137.4, 137.3, 136.4, 135.3, 124.7, 124.6, 124.3, 123.6, 119.0, 91.6, 98.5, 86.6, 84.5, 77.5, 77.2, 76.8, 66.4, 60.6, 53.6, 34.0, 19.0, 11.7; FTIR-ATR v max/cm−1 2035 (Fe=CO); HRMS (ESI+) m/z: [M + H]+ calc f= C21H19FeO3S 429.0246; found 429.0246.

Tricarbonyl[(cyclohexa-2,4-dien-1-yl)]azulene-1-ylthio)trisopropylsilane[iron (16). Synthesized according to general procedure B using azulene derivative 10 (11.2 mg, 0.0363 mmol), iron complex 6 (14.5 mg, 0.0398 mmol), and NaHCO3 (6.1 mg, 0.073 mmol) in 0.5 mL acetonitrile. The product was purified by reversed-phase flash chromatography (MeOH/H2O 70:30 → 100%) yielding 16 as a green sticky solid (133 mg, 70%);1H NMR (400 MHz, chloroform-d) δ 8.45 (d, J = 9.6 Hz, 1H), 8.15 (d, J = 9.6 Hz, 1H), 7.81 (s, 1H), 7.56 (app t, J = 9.8 Hz, 1H), 7.15 (app t, J = 9.9 Hz, 1H), 7.12 (app t, J = 9.9 Hz, 1H), 5.61–5.57 (m, 1H), 5.48 (dd, J = 6.0, 4.1, 1.5 Hz, 1H), 3.96 (app dt, J = 11.2, 3.6 Hz, 1H), 3.27–3.23 (m, 2H), 2.51 (dd, J = 15.1, 11.2, 3.8 Hz, 1H), 1.79–1.72 (m, 1H), 1.21–1.19 (m, 2H); 13C{1H} NMR (101 MHz, chloroform-d) δ 212.2, 142.7, 139.0, 137.2, 136.5, 136.3, 135.1, 133.7, 123.8, 123.7, 110.1, 103.1, 95.2, 86.5, 84.8, 77.5, 77.2, 76.8, 66.4, 60.6, 53.6, 34.0, 19.0, 11.7; FTIR-ATR v max/cm−1 2133 (C≡C)° (Fe=CO); HRMS (ESI+) m/z: [M + H]+ calc f= C23H17FeO3S 429.0239; found 429.0239.
(MeOH/H2O 95:5), yielding an equimolar mixture of diastereomers 18 and 18′ as a green sticky solid (45.8 mg, 83%); 1H NMR (400 MHz, chloroform-d) δ 8.14 (d, J = 9.5 Hz, 2H), 7.64–7.59 (m, 2H), 7.52–7.40 (m, 4H), 7.19 (d, J = 10.2 Hz, 2H), 5.68–5.60 (m, 20H), 5.53–5.43 (m, 2H), 4.01 (app dt, J = 11.2, 3.6 Hz, 2H), 3.35–3.24 (m, 4H), 2.60–2.46 (m, 2H), 1.86–1.75 (m, 2H). 13C{1H} NMR (101 MHz, chloroform-d) δ 212.3, 151.7, 151.2, 134.9, 134.9, 134.3, 134.3, 134.2, 134.2, 128.1, 128.1, 128.1, 122.0, 86.3, 86.2, 84.7, 84.7, 67.1, 67.1, 60.8, 60.8, 36.0, 36.0, 34.0, 33.9; FT-IR-ATR νmax/cm−1 2037 (Fe–CO), 1942 (Fe–CO); HRMS (ESI+) m/z: [M + H]+ calc for C11H12FeO2 417.1153; found 417.1155.

Tricarbonyl[7-isopropyl-3-(4-methoxy cyclohexa-2,4-dien-1-yl)-1,4-dimethylazulene]iron (27). Synthesized according to general procedure A using guaiacil 1 (21.8 mg, 0.110 mmol), iron complex 2 (39.4 mg, 0.110 mmol), and NaHCO3 (12.6 mg, 0.150 mmol), with a reaction time of 16 h. The product was purified by reversed-phase chromatography (MeOH/H2O, 60:40 → 85:15), yielding 27 as a blue solid (41.4 mg, 93%); mp 101–103 °C. 1H NMR (400 MHz, chloroform-d) δ 8.01 (d, J = 2.2 Hz, 1H), 7.49 (s, 1H), 7.22 (dd, J = 10.6, 2.2 Hz, 1H), 6.79 (d, J = 10.7 Hz, 1H), 5.26 (dd, J = 6.6, 2.4 Hz, 1H), 4.22 (app dt, J = 11.0, 3.6 Hz, 1H), 3.74 (s, 3H), 3.50 (app dt, J = 3.9, 2.3 Hz, 1H), 2.99 (hept, J = 6.9 Hz, 1H), 2.90 (s, 3H), 2.85 (dd, J = 6.6, 3.4 Hz, 1H), 2.60 (s, 3H), 2.44 (ddd, J = 14.8, 10.9, 3.9 Hz, 1H), 1.85 (ddd, J = 14.7, 3.7, 2.3 Hz, 1H), 1.32 (d, J = 6.9 Hz, 6H). 13C{1H} NMR (101 MHz, chloroform-d) δ 211.7, 144.7, 140.3, 139.6, 138.5, 136.6, 134.6, 133.7, 133.0, 131.1, 126.7, 124.9, 67.3, 57.5, 54.6, 53.6, 38.0, 37.7, 36.2, 27.5, 24.3, 13.2; FT-IR-ATR νmax/cm−1 2036 (Fe–CO), 1958 (Fe–CO); HRMS (ESI+) m/z: [M + H]+ calc for C11H12FeO2 447.1258; found 447.1258.

Tricarbonylmethyl 5-(3-formyl-5-methylazulen-1-yl)cyclohexa-1,3-diene-1-carboxylate (25). Synthesized according to general procedure A using azulene derivative 19 (23.4 mg, 0.110 mmol), complex 2 (42.2 mg, 0.16 mmol), and NaHCO3 (12.6 mg, 0.150 mmol), with a reaction time of 16 h. The product was purified by reversed-phase chromatography (MeOH/H2O 60:40 → 85:15), yielding 25 as a purple solid (27.3 mg, 56%); mp 74–76 °C; 1H NMR (400 MHz, chloroform-d) δ 10.27 (s, 1H), 9.60 (s, 1H), 8.10 (s, 1H), 7.57 (dd, J = 10.8, 2.2 Hz, 1H), 7.35 (dd, J = 10.7 Hz, 1H), 6.73 (d, J = 4.3 Hz, 1H), 5.66 (dd, J = 6.3, 4.4 Hz, 1H), 4.48 (app dt, J = 11.4, 4.4 Hz, 1H), 3.72 (s, 3H), 3.44 (ddd, J = 6.4, 3.2, 1.4 Hz, 1H), 3.15 (hept, J = 6.9 Hz, 1H), 3.07 (s, 3H), 2.91 (dd, J = 15.1, 11.3 Hz, 1H), 1.54 (dd, J = 15.1, 4.4 Hz, 1H), 1.37 (d, J = 6.9 Hz, 6H). 13C{1H} NMR (101 MHz, chloroform-d) δ 168.9, 162.4, 158.4, 142.9, 129.8, 126.2, 124.5, 120.4, 118.2, 117.3, 117.2, 113.5, 133.0, 124.1, 89.1, 84.8, 67.7, 62.4, 51.7, 39.3, 37.9, 33.8, 27.5, 24.4. Signal for Fe–CO not seen; FT-IR-ATR νmax/cm−1 2050 (Fe–CO), 1974 (Fe–CO), 1707 (C=O), 1643 (C=O); HRMS (ESI+) m/z: [M + H]+ calc for C12H12FeO2 489.1000; found 489.1016.

Tricarbonylmethyl 5-(3-isopropyl-3,8-dimethyl-2,4,4,5,5-tetramethyl-1,3-dioxaborol-2-yl)-1,4-dimethylazulen-1-yl)cyclohexa-1,3-diene-1-carboxylate (26). Synthesized according to general procedure A using guaiacil 1 (21.8 mg, 0.110 mmol), iron complex 6 (36.4 mg, 0.100 mmol), and NaHCO3 (12.6 mg, 0.150 mmol), with a reaction time of 16 h. The product was purified by reversed-phase chromatography (MeOH/H2O 60:40 → 90:10), yielding 26 as a green sticky solid (45.6 mg, 83%); 1H NMR (400 MHz, chloroform-d) δ 8.01 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 10.6, 2.1 Hz, 1H), 6.83 (d, J = 10.6 Hz, 1H), 6.30 (d, J = 4.3 Hz, 1H), 5.39 (dd, J = 6.5, 4.3 Hz, 1H), 4.82 (ddd, J = 11.0, 5.7, 2.6 Hz, 1H), 3.73 (s, 3H), 3.37 (ddd, J = 6.4, 2.6, 1.2 Hz, 1H), 3.00 (s, 3H), 2.97 (hept, J = 6.9 Hz, 1H), 2.76 (dd, J = 15.0, 11.1 Hz, 1H), 2.64 (s, 3H), 1.88 (ddd, J = 15.0, 5.8 Hz, 1H), 1.48 (s, 6H), 1.44 (s, 6H), 1.31 (d, J = 6.9 Hz, 6H). 13C{1H} NMR (101 MHz, chloroform-d) δ 210.8 (br), 173.0, 144.0, 140.0, 139.3, 130.5, 134.8, 133.6, 133.2, 132.7, 127.6, 87.9, 85.6, 84.0, 74.1, 62.9, 51.7, 41.4, 37.6, 29.3, 28.5, 25.9, 25.4, 24.3, 13.2. Signal for C=O not seen; FT-IR-ATR νmax/cm−1 2045 (Fe–CO), 1968 (Fe–CO), 1708 (CO); HRMS (ESI+) m/z: [M + H]+ calc for C13H12FeO2 501.2059; found 501.2049.
when the CDCl₃ was filtered through a plug of basic aluminum oxide prior to use; ¹H NMR (400 MHz, chloroform-d) δ 8.13 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 10.7, 2.1 Hz, 1H), 6.98 (d, J = 10.7 Hz, 1H), 6.33 (d, J = 4.3 Hz, 1H), 5.66 (dd, J = 6.5, 4.3 Hz, 1H), 4.97 (ddd, J = 11.0, 6.4, 2.5 Hz, 1H), 3.74 (s, 3H), 3.13 (d, J = 5.6 Hz, 1H), 3.09–2.97 (m, 4H), 2.65 (dd, J = 14.8, 11.2 Hz, 1H), 2.59 (s, 3H), 1.97 (d, J = 14.8, 6.3 Hz, 1H), 1.33 (d, J = 6.9 Hz, 6H). ¹³C{¹H} NMR (101 MHz, chloroform-d) δ 210.9 (br), 173.0, 143.3, 141.8, 136.3, 134.9, 133.8, 133.2, 129.0, 128.8, 126.4, 105.7, 88.9, 86.4, 67.5, 63.2, 51.8, 40.5, 37.7, 29.0, 26.8, 24.7, 16.3; FT-IR: v/cm⁻¹ 2048 (Fe–CO), 1972 (Fe–CO), 1706 (C=O); HRMS (ESI+) m/z: [M + H⁺]⁺ calculated for C₂₆H₂₆FeIO₅ 601.0174; found 601.0177.

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Tricarbonyl[5-(2-bromo-5-isopropyl-3,8-dimethyl-azulenyl-1-yl)cyclohexa-1,3-diene-1-carboxylate]iron (31). Synthesized according to general procedure A using azulene derivative 22 (10.0 mg, 0.0361 mmol, iron complex synthesized according to general procedure A using azulene derivative prior to use; ¹H NMR (400 MHz, chloroform-d) δ 8.13 (d, J = 2.2 Hz, 1H), 7.47 (s, 1H), 7.33 (dd, J = 10.7, 2.2 Hz, 1H), 7.10 (dd, J = 10.1, 3.0, 1.2 Hz, 1H), 6.92 (d, J = 10.7 Hz, 1H), 6.16 (dd, J = 10.1, 2.5 Hz, 1H), 4.76 (app ddt, J = 7.9, 5.0, 2.8 Hz, 1H), 3.05 (hept, J = 6.9, 1H) 3.02 (s, 3H), 2.65–2.57 (m, 4H), 2.55–2.44 (m, 2H), 2.23–2.11 (m, 1H), 1.35 (d, J = 6.9 Hz, 6H); ¹³C{¹H} NMR (101 MHz, chloroform-d) δ 199.9, 155.4, 144.7, 140.1, 138.1, 137.8, 135.2, 131.4, 131.6, 128.8, 128.0, 127.3, 125.0, 37.8, 37.4, 37.0, 33.9, 27.5, 24.7, 13.1; FT-IR: v/cm⁻¹ 1679 (C=O); HRMS (ESI+) m/z: [M + H⁺]⁺ calculated for C₃₀H₂₃O₃ 479.1593; found 479.1594.

1,3-Diphenylazulene (36). To a 5 mL microwave vial equipped with a stir bar, containing 27.4 mg (0.0970 mmol) of compound 33, was added 24.2 mg (0.107 mmol) DDO. The vial was purged under an atmosphere of nitrogen. Toluene (1.0 mL) was added, and the solution was stirred at room temperature for 40 min. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with 1 M aqueous NaOH (3 × 20 mL) followed by brine (1 × 20 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography (petroleum ether/EtOAc 99:1), yielding 36 as a blue-green solid (22.3 mg, 82%). ¹H NMR (400 MHz, chloroform-d) δ 8.57 (dd, J = 9.8, 1.2 Hz, 2H), 8.15 (s, 1H), 7.69–7.66 (m, 4H), 7.60 (s, J = 9.8, 1.2 Hz, 1H), 7.56–7.50 (m, 4H), 7.40 (app ddt, J = 7.9, 6.9, 1.3 Hz, 2H), 7.14 (dd, J = 9.8, 9.8 Hz, 2H); ¹³C{¹H} NMR (101 MHz, chloroform-d) δ 139.1, 137.4, 137.3, 136.8, 136.3, 130.7, 130.0, 128.8, 126.6, 126.3. Analysis data are in accordance with published data for this compound.¹⁶b

{(7α,11αR)-4-isopropyl-2-methyl-7,7a,8,10,11,11a-hexahydro-9H-naphtho[1,2,3-c]azulen-9-one (37). In a 2 mL microwave vial equipped with a stir bar, compound 35 (9.3 mg, 0.032 mmol) was dissolved in THF (1 mL). The vial was capped and cooled in an ice bath. t-BuOK was added to a 1 M solution in THF (100 mL, 0.100 mmol). The solution was left to stir at 0 °C for 20 min, after which it was poured into 1 M aqueous HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the solvent was removed under a stream of nitrogen. The crude product was purified by flash chromatography (petroleum ether/EtOAc 90:10), yielding 37 as a blue sticky oil (3.6 mg, 39%); ¹H NMR (400 MHz, chloroform-d) δ 8.09 (d, J = 1.8 Hz, 1H), 7.54 (s, 1H), 7.36 (dd, J = 10.5, 1.8 Hz, 1H), 6.77 (d, J = 10.5 Hz, 1H), 6.31 (app dt, J = 5.7, 4.5 Hz, 1H), 3.25 (dd, J = 16.8, 4.4 Hz, 1H), 3.04 (app ddt, J = 9.6, 1.9 Hz, 1H), 2.91 (dd, J = 16.8, 6.6 Hz, 1H), 2.84–2.75 (m, 1H), 2.67 (s, 3H), 2.49–2.42 (m, 2H), 2.41–2.36 (m, 2H), 2.32 (dd, J = 14.3, 8.6 Hz, 1H), 2.25–2.18 (m, 1H), 1.35 (d, J = 6.9 Hz, 6H); ¹³C{¹H} NMR (101 MHz, chloroform-d) δ 212.3, 144.0, 139.3, 135.8, 134.2, 133.4, 133.3, 132.8, 125.8, 124.5, 122.7, 44.6, 38.7, 38.7, 38.3, 37.7, 34.7, 30.4, 24.90, 24.91, 12.9; FT-IR: v/cm⁻¹ 1709 (C=O); HRMS (ESI+) m/z: [M + H⁺]⁺ calculated for C₂₆H₂₃O₃ 393.1904; found 393.1904.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge from https://pubs.acs.org/doi/10.1021/acs.joc.0c01412

Spectroscopic data for all products; NMR assignments and stereochemical elucidation of 37; colorimetric response to TFA and UV−vis/fluorescence spectra for 31.
selected compounds; and emission spectrum of lamp used for photolytic decompositions (PDF)

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All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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