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Iridium-Catalyzed Dehydrogenative Silylation of Azulenes Based on Regioselective C−H Bond Activation

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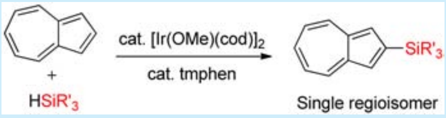
S *Supporting Information*

ABSTRACT: Use of an iridium catalyst allowed the efficient dehydrogenative functionalization of C−H bonds of azulenes with the production of hydrogen as the sole byproduct. The reaction occurred with excellent chemo- and regioselectivities to provide 2-silylazulenes even without any directing groups. Effective conjugation through the 2-position of the azulene ring was demonstrated by the unique stimuli-responsiveness against an acid−base reaction.



Azulenes, which show unique photophysical and redox properties derived from their unusual dipolar and π-electron polarizations, are promising components for the construction of advanced functional materials.[1] The development of simple and efficient chemical modification methods would provide an opportunity to disclose their novel electro- and physical properties and further extend their utility as new functional molecules. Since azulene has a dipole moment between the 6 and 2 positions, selective functionalizations at these positions are highly desirable to emphasize the dipolar structure directly.[2] However, this is generally difficult due to the uniquely localized HOMO and LUMO orbitals. The basic reactivity of azulene can be understood by its resonance structure and the large HOMO and LUMO coefficients at 1-, 3- (for HOMO) and 4-, 8-positions (for LUMO), respectively (Figure 1). Therefore, electrophilic functionalization, such as bromination and formylation, occurs at the 1- and 3-positions, whereas nucleophilic addition preferentially occurs at the 4- and 8-positions.[3] Selective functionalization at the 2- and 6-positions usually requires multistep transformations, which sometimes includes the construction of the azulene skeleton itself.[4]

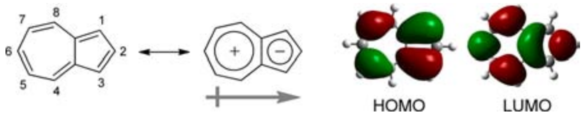
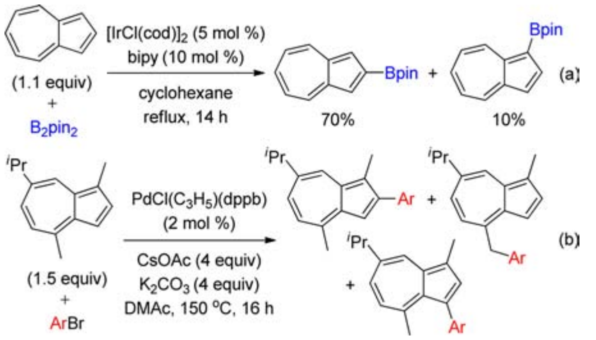


Figure 1. Dipolar structure and HOMO/LUMO orbital distributions of azulene.

Recently, catalytic direct functionalization of unactivated C−H bonds has received considerable attention as a practical preparation method for substituted aromatics. Utilizing this type of transformation, two methods for functionalization at the 2-position of the azulene ring have been reported, i.e., iridium-catalyzed direct borylation of $C(sp^2)$−H bonds of azulenes with bis (pinacolato)diboron (Scheme 1a)[5a,b] and palladium-catalyzed direct arylation of $C(sp^2)$−H and $C(sp^3)$−H bonds of guaiazulene with Ar−Br (Scheme 1b).[5c,d] These methods are highly useful; however, functionalization occurs at both the 1- and 2-positions to afford a mixture of several regioisomers with undesirable substitution patterns. These regioisomers must be separated for use as building blocks, which decreases the synthetic utility of these two methods.

Scheme 1. Direct Functionalization of C−H Bonds at the 2-Position of Azulene Derivatives



We have developed transition-metal-catalyzed dehydrogenative silylation, borylation, and phosphination of $C(sp^2)$−H or $C(sp^3)$−H bonds as powerful tools for the construction of complex heteroaromatic compounds.[6] In 2015, we and Hartwig independently reported iridium-catalyzed intermolecular dehydrogenative silylation of aromatic compounds without directing groups.[7,8] The reaction proceeded with opposite chemo- and site-selectivity compared to that observed for general electrophilic functionalization of aromatic compounds. Therefore, we envisioned that the iridium-catalyzed dehydrogenative silylation of $C(sp^2)$−H bonds of azulenes would allow a straightforward

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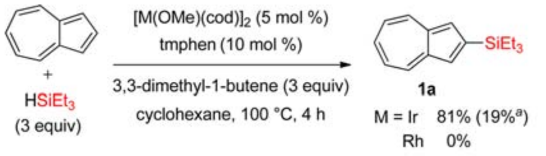
modification of their electronic nature and, hence, of the properties of the resulting azulene derivatives in a single step. The current study describes the highly selective dehydrogenative functionalization enabling the direct use of azulenes as substrates and the production of hydrogen as the sole byproduct.

Treatment of azulene with 3 equiv of triethylsilane and 3,3-dimethyl-1-butene as a hydrogen acceptor in the presence of $[Ir(OMe)(cod)]_2$ as a catalyst and 3,4,7,8-tetramethyl-1,10-phenanthroline (hereafter referred to as "tmphen") as a ligand in cyclohexane (0.20 M) afforded 2-silylazulene **1a** as a single regioisomer in 81% yield (eq 1). In sharp contrast with the previous intermolecular dehydrogenative silylation,[9a−h] the reaction proceeded efficiently with small excess amounts of triethylsilane. The use of $[Rh(OMe)(cod)]_2$ in place of the iridium catalyst completely shut down the reaction. In contrast to our previous report on the dehydrogenative silylation of naphthalene,[7] **1a** was obtained in 19% yield without any hydrogen acceptors. Other transition-metal complexes, including rhenium, ruthenium, rhodium, and platinum catalysts, were totally ineffective with the recovery of most of the azulene used.[10]

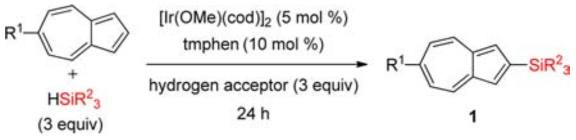


(1)

[a] Yield of **1a** in the absence of 3,3-dimethyl-1-butene.

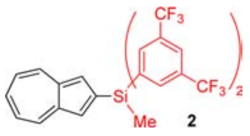
Using the combination of $[Ir(OMe)(cod)]_2$ with tmphen as the catalyst and ligand, the effect of the substitution pattern of silanes was investigated (Table 1). Aryldimethylsilanes possessing electron-donating and -withdrawing substituents reacted to furnish the corresponding 2-silylazulenes **1b−d** in moderate yields (entries 1−3), which implied that variation of the electronic properties of the silane had little influence on the reactivity. The use of highly electron-deficient 3,5-(trifluoromethylphenyl)dimethylsilane as a silane source resulted in a decrease of the corresponding coupling product **1e**, along with diarylmethylsilane **2** in 9% yield (entry 4). This unexpected coupling product **2** might be formed via the competitive disproportionation of 3,5-(trifluoromethylphenyl)-dimethylsilane during the dehydrogenative silylation.[11] Benzyldimethylsilane was also a suitable substrate to afford 2-silylazulene **1f** in 79% yield even at 100 °C (entry 5). In this reaction, slow addition of silane was required to obtain the coupling product in good yield. 6-Heptylazulene can be used in place of azulene to provide the corresponding 2-silylazulene **1g** in 74% yield.[12] Note that 2-silylazulenes were obtained selectively without forming their regioisomers, including 1-silylazulenes, in all of the reactions listed in Table 1. 2-(Dimethylsilyl)thiophene and alkoxysilanes such as silatrane and triethoxysilane were not applicable as silane sources.

Table 1. Iridium-Catalyzed Regioselective Dehydrogenative Silylation of Azulenes with Hydrosilanes



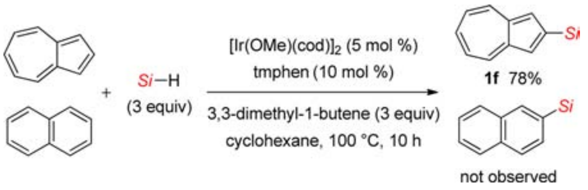
entry	method[a]	temp (°C)	R^1	SiR^2_3	product	yield (%)
1[b]	A	125	H	$SiMe_2Ph$	**1b**	67
2[b]	A	125	H	$SiMe_2(4\text{-}MeOC_6H_4)$	**1c**	66
3	A	125	H	$SiMe_2(4\text{-}CF_3C_6H_4)$	**1d**	61
4	A	150	H	$SiMe_2(3,5\text{-}(CF_3)_2C_6H_3)$	**1e**	41[c]
5[b]	B	100	H	$SiMe_2Bn$	**1f**	79
6[d]	B	100	$^nC_7H_{15}$	$SiEt_3$	**1g**	74

[a] Method A: Norbornene (hydrogen acceptor) in octane. Method B: 3,3-Dimethyl-1-butene (hydrogen acceptor) in cyclohexane. [b] For 10 h. [c] Compound **2** was obtained as a byproduct in 9%. [d] For 4 h.



During these investigations, selective dehydrogenative silylation of azulene was observed in the presence of other aromatic compounds. For example, competition experiments with naphthalene in the same flask, which is the structural isomer of azulene, produced 2-silylazulene selectively with naphthalene recovered intact (Scheme 2). Similar selective silylation of azulene was observed in the reactions with pyrene, anthracene, phenanthrene, and benzene.

Scheme 2. Selective Dehydrogenative Silylation of Azulene in the Presence of Naphthalene (*Si* = $SiMe_2Bn$)



In our previous study on the dehydrogenative silylation of polycyclic aromatic hydrocarbons, electron-deficient substrates were more efficiently silylated.[7] However, the dehydrogenative silylation of $C(sp^2)−H$ bonds at the electron-deficient seven-membered ring of azulene was not observed under the present reaction conditions. This reactivity might be explained by considering the ease of the π-complexation between an iridium center and the five-membered ring of azulene. Azulene has a fused structure of a cyclopentadienyl anion ($Cp^−$) and cycloheptatrienyl cation, and $Cp^−$ is well-known as a good ligand for various transition-metal complexes. Although C−H bond activation without using a heteroatom-containing directing group is generally difficult,[13] the above interaction might fix the iridium center near the C−H bond on the five-membered ring and promote this energetically unfavorable step (see intermediate **B** in Scheme 3).[14]

Taking these observations into consideration, a tentative reaction mechanism is proposed in Scheme 3 (tmphen ligands are omitted for clarity). The *Ir*−OMe complex is initially converted to an *Ir*−H species via oxidative addition to hydrosilane followed by the reductive elimination of *Si*−OMe.[15] This species is then oxidatively added to hydrosilane, inserted onto 3,3-dimethyl-1-butene, and reductively eliminated to furnish the *Ir*−*Si* species **A**.[16] Oxidative addition of **A** to the $C(sp^2)−H$ bond at the 2-position of azulene, which can be promoted by the facile interaction of the iridium center with the $Cp^−$ moiety of azulene, was followed by reductive elimination to afford the corresponding 2-silylazulenes. Chemoselective

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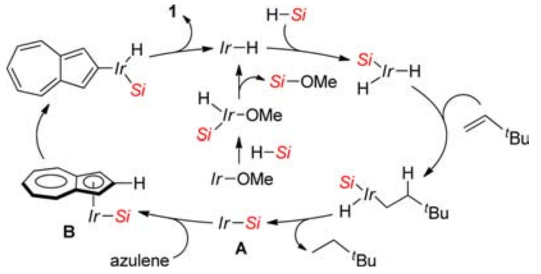
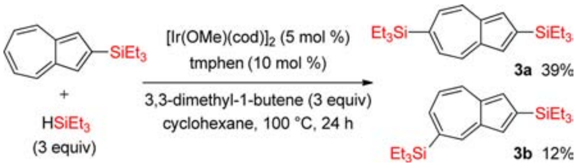
Scheme 3. Plausible Reaction Mechanism (*Si* = SiR_3)



silylation of azulene in the presence of other polycyclic aromatic hydrocarbons observed in Scheme 2 can be explained by predominant formation of the Cp−*Ir* intermediate **B**.[17] Furthermore, steric factors dominated the site-selectivity of the reaction to provide 2-silylazulenes exclusively via regioselective C−H bond activation at the least sterically hindered 2-position.

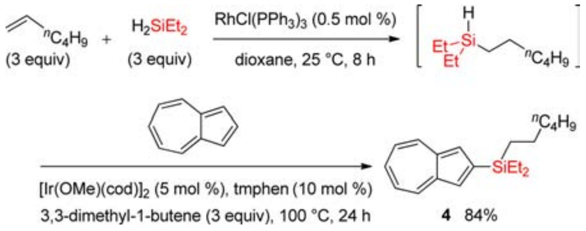
In the course of these studies, unexpected formation of 2,6-disilyl- and 2,5-disilylazulenes **3a** and **3b** was observed in the reaction of azulene with triethylsilane in a reduced amount of cyclohexane (1.0 M). These disilylated azulenes were likely formed via two sequential dehydrogenative silylations on the five- and seven-membered rings of azulene. In fact, treatment of 2-silylazulene **1a** with triethylsilane in the presence of the iridium complex furnished disilylazulenes **3a** and **3b** in 39% and 12% yields, respectively (Scheme 4).

Scheme 4. Iridium-Catalyzed Dehydrogenative Silylation of C(sp^2)−H Bonds on the Seven-Membered Ring of Azulene



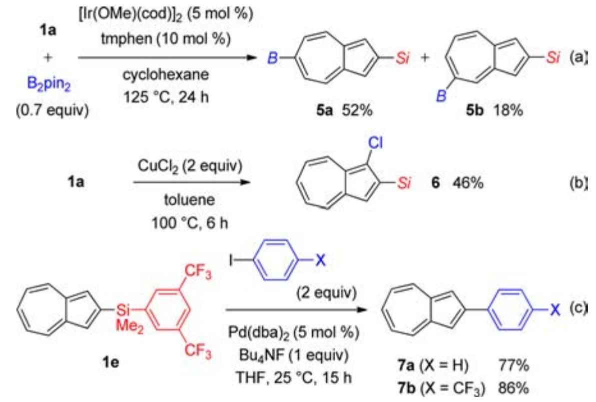
Unfortunately, dihydrosilanes, including Et_2SiH_2, Ph_2SiH_2, and $PhMeSiH_2$, were not applicable, and the scope of the silane was limited to monohydrosilanes under the current reaction conditions. Taking advantage of this reactivity difference, a cascade reaction initiated by hydrosilylation with an olefin followed by the dehydrogenative silylation of azulene was carried out. First, dihydrosilane Et_2SiH_2 was treated with 1-hexene in the presence of Wilkinson catalyst, $RhCl(PPh_3)_3$, at 25 °C for 8 h.[18] Subsequently, the dehydrogenative silylation step was performed under the current iridium-catalyzed reaction conditions to furnish the expected three-component coupling product, 2-silylazulene **4**, in 84% yield (Scheme 5).

Scheme 5. Three-Component Coupling Reaction Leading to 2-Silylazulene 4



The resulting 2-silylazulene can be utilized for further derivatization of the azulene ring. Treatment of 2-silylazulene **1a** with bis(pinacolato)diboron in the presence of an iridium catalyst furnished 6-boryl-2-silyl- and 5-boryl-2-silylazulenes **5a** and **5b** in 52% and 18% yields, respectively (Scheme 6a).[5a,b] The borylation occurred preferentially at the 6-position and followed similar selectivity as was observed in the silylation of the 7-membered ring (see Scheme 4). Chlorination of **1a** using $CuCl_2$ afforded 1-chloro-2-silylazulene **6** in 46% yield (Scheme 6b). Note that this chlorination without affecting the silyl group functionality cannot be attained by the typical chlorination schemes using chlorine or *N*-chlorosuccinimide. 2-Arylazulenes **7a** and **7b** were obtained by the palladium-catalyzed Hiyama cross-coupling reaction of 2-silylazulene **1e** with aryl iodides,[19,20] showing the potential utility of the present reaction toward the effective expansion of azulene's *π*-conjugated system (Scheme 6c).

Scheme 6. Synthetic Derivatization of 2-Silylazulenes 1a and 1e (*Si* and *B* = $SiEt_3$ and Bpin, Respectively)



Effective conjugation through the 2-position of the azulene ring was confirmed by the longest absorption maximum peak for **7b** (385 nm), which was red-shifted by 15 nm compared with that of the regioisomer 1-(4-(trifluoromethyl)phenyl)azulene **7b′** (Figure 2).[21] Moreover, the unique stimuli-responsiveness was demonstrated by the reversible color change against acid−base reaction of **7b**.[22] A significant change in the absorption was found upon addition of TFA to a solution of **7b** in CH_2Cl_2. An absorption at 427 nm appeared along with an instant color

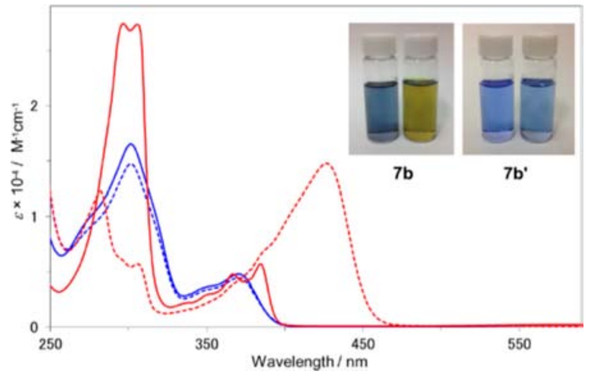


Figure 2. UV−vis spectra in CH_2Cl_2 of **7b** (red) and **7b′** (blue) for neutral state (solid line) and upon the addition of CF_3CO_2H (dashed line). Inset: photographs of the neutral state (left) and after protonation by CF_3CO_2H (right) for each compound.

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change of the solution from blue to yellow. In contrast, the regioisomer 1-arylazulene **7b**′ did not show such behavior, which clearly implies the utility of the current regioselective functionalization at the 2-position of the azulene ring. These differences can be explained by the perturbation of the π-conjugation upon the formation of the azulenium cation. It is known that protonation of azulene derivatives occurs at the 1- and/or 3-position on the electron-rich five-membered ring. Therefore, the structure of 1-arylazulene **7b**′ might not be effective for the conjugation since it cannot retain the planar structure after the protonation.

In conclusion, a novel straightforward functionalization of C−H bonds at the 2-position of azulene based on regioselective dehydrogenative silylation has been described. The current method provides a practical route for the construction of azulene's uniquely polarized π-system, which is difficult to access by conventional approaches.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Other transition-metal complexes, including $RhCl(PPh_3)_3$, $[Rh(OAc)_2]_2$, $Re_2(CO)_{10}$, $Ru_3(CO)_{12}$, and $Ir_4(CO)_{12}$, did not promote the desired reaction, and most of azulene was recovered.

(11) Disproportionation of **1e** to **2** via the exchange of the methyl and 3,5-di(trifluoromethyl)phenyl groups was not observed under the current conditions, which implies that the disproportionation occurred before dehydrogenative silylation of the C−H bond.

(12) The reaction of guaiazulene with triethylsilane under the reaction conditions noted in Table 1, entry 5, afforded the corresponding 2-silylazulene as a single regioisomer in 22% yield.

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(20) 2-Silylazulene **2** can be also utilized as a coupling partner to afford **7a** in 66% yield by the reaction with iodobenzene.

(21) For **7b**: $\lambda_{max} = 297$ nm ($\varepsilon = 2.7 \times 10^4$), 306 nm ($\varepsilon = 2.7 \times 10^4$), 367 nm ($\varepsilon = 0.48 \times 10^4$), 385 nm ($\varepsilon = 0.57 \times 10^4$). For **7b**′: $\lambda_{max} = 302$ ($\varepsilon = 1.7 \times 10^4$), 370 ($\varepsilon = 0.48 \times 10^4$).

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