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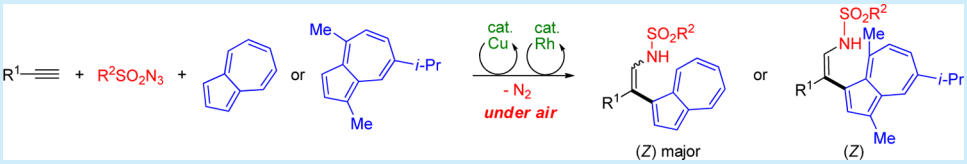
Diastereoselective *N*-Sulfonylaminoalkenylation of Azulenes from Terminal Alkynes and Azides via *N*-Sulfonyl-1,2,3-triazoles

Sangjune Park, Woo-Soon Yong, Sanghyuck Kim, and Phil Ho Lee*

Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea

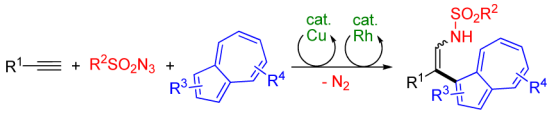
Supporting Information



ABSTRACT: The development of rhodium-catalyzed diastereoselective *N*-sulfonylaminoalkenylation of azulenes using *N*-sulfonyltriazoles is described. This procedure can be successfully applied to rhodium-catalyzed diastereoselective *N*-sulfonylaminoalkenylation of azulenes starting from terminal alkynes and *N*-sulfonylazides via a three-component semi-one-pot process.

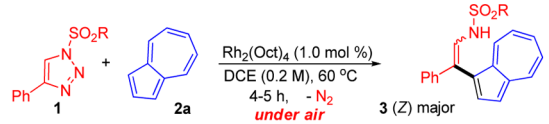
Azulenes, which are known to be a class of nonbenzenoid aromatic hydrocarbons, have attracted notable attention because of their significance as natural products,[1] biologically active compounds,[2] and molecular materials.[3] Thus, development of efficient synthetic methods of these compounds from readily available starting materials has been in continuous demand.[4] Although Hafner and co-workers reported a novel synthetic approach of azulene in one pot,[5] introduction of valuable substituents onto azulene have limitations due to its unusual reactivity caused by the polarized π-electron system. For this reason, synthetic strategies of azulene through an introduction of a new functional group and its transformation are extremely desirable for the preparation of azulene derivatives. Herein, we report diastereoselective introduction of an enamine functionality on the azulenes from terminal alkynes and azides via *N*-sulfonyl-1,2,3-triazoles (Scheme 1).[6]

Scheme 1. Aminoalkenylation of Azulenes



First, triazoles **1** having a diversity of sulfonyl groups at the N1 were examined in the reaction with azulene (**2a**) (Table 1). A variation of the sulfonyl groups at the N1 of triazoles **1** did not affect the reaction efficiency. Methane-, *n*-butane-, and isopropanesulfonyl triazoles[7] selectively afforded the *N*-sulfonylaminoalkenylated azulenes at the C1-position in excellent yields ranging from 91% and 96% (entries 1−3). *N*-[(4-Methoxybenzene)sulfonyl]triazole **1e** is slightly less reactive (entry 5). In contrast, (benzenesulfonyl)triazoles having electron-withdrawing chloro and trifluoromethyl groups gave the desired azulenes **3f** and **3g** in excellent yields and diastereoselectivities (entries 6 and 7). The optimal reaction

Table 1. Reaction Optimization[a]



entry	R	3	yield (%)	entry	R	3	yield (%)
1	Me	**3a**	94 (8.3:1)	4	4-Me-C_6H_4	**3d**	96 (10:1)
2	*n*-Bu	**3b**	96 (10:1)	5	4-MeO-C_6H_4	**3e**	83 (10:1)
3	*i*-Pr	**3c**	91 (10:1)	6	4-Cl-C_6H_4	**3f**	90 (12:1)
				7	4-CF_3-C_6H_4	**3g**	94 (12:1)

[a] **1** (0.2 mmol) and **2a** (0.3 mmol) in the presence of $Rh_2(Oct)_4$ (1.0 mol %) were heated in DCE (1.0 mL) at 60 °C for 4−5 h under air. Ratios in parentheses are *Z*/*E* ratios.

conditions could be obtained with $Rh_2(Oct)_4$ (1.0 mol %) in DCE (0.2 M) at 60 °C after 2 h under air and selectively provided the *N*-sulfonylaminoalkenylated product **3d** in 96% (*Z*/*E* = 10:1) yield (see the Supporting Information).

Having established the optimal reaction conditions, we next examined the scope of this new reaction with respect to variously substituted 1-tosyl-1,2,3-triazoles **1** to react with azulene (**2a**) (Scheme 2). Electronic variation of substituents at the arene moiety of 4-aryl-1-tosyl-1,2,3-trazoles **1** had little effect on the reaction efficiency. In fact, 1-[(*N*-sulfonylamino)alkenyl]-azulenes **1h** and **1i** having electron-donating methyl groups on the phenyl ring were selectively obtained in good to excellent yields. Triazoles having methoxy substituents on the phenyl ring were selectively alkenylated to the desired azulenes **3j** (84%) and **3k** (94%). Halide functional groups commonly used in cross-coupling reactions were tolerated. For example, substrates possessing chloro (**1l** and **1m**) and bromo (**1n**) groups were

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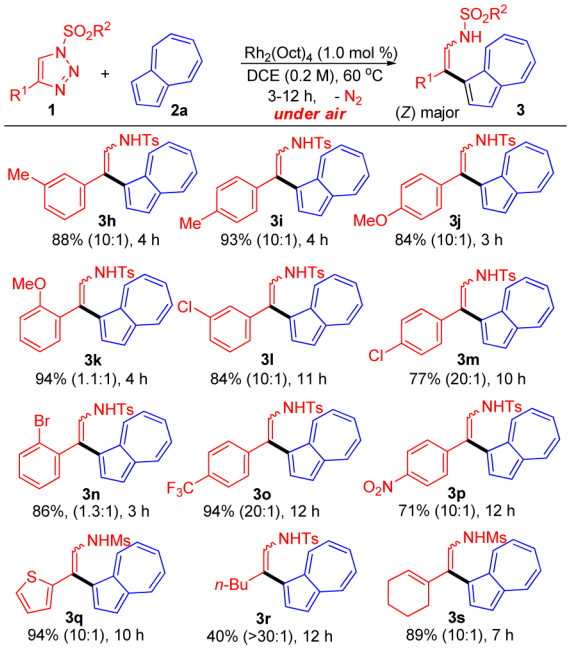
Scheme 2. Aminoalkenylation of Azulenes[a]

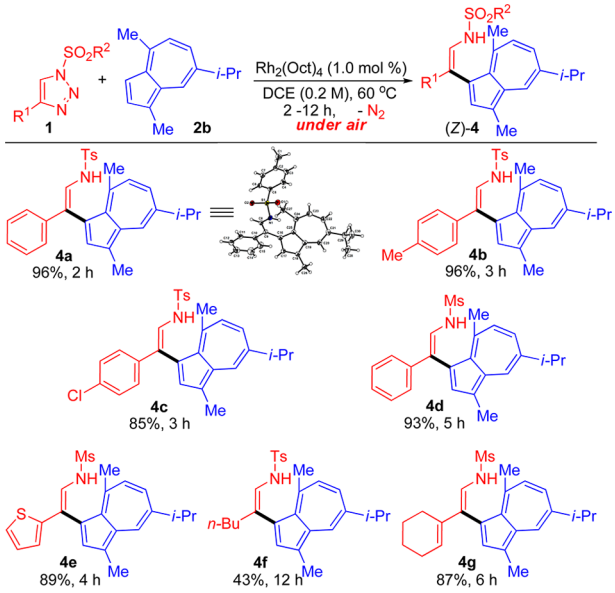


[a]**1** (0.2 mmol) and **2a** (0.3 mmol) in the presence of $Rh_2(Oct)_4$ (1.0 mol %) were heated in DCE (1.0 mL) at 60 °C for 3−12 h under air. Ratios in parentheses are *Z*/*E* ratios.

all smoothly aminoalkenylated in yields ranging from 77% and 86%. However, introduction of substituents such as bromide and methoxy at ortho position on the phenyl ring decreased the diastereoselectivities due to steric reason between phenyl and azulenyl groups. Electron-withdrawing trifluoromethyl-substituted triazole **1o** underwent *N*-sulfonylaminoalkenylation in 94% yield. It is noteworthy that triazoles having electron-withdrawing chloro and trifluoromethyl groups at the C4 position on the phenyl ring gave excellent selectivities (*Z*/*E* = 20:1). 4-Nitrophenyl-substituted triazole **1p** was less reactive, producing the desired product **3p** in 71% yield (*Z*/*E* = 10:1). NOE experiments indicate that the major isomer of **3p** is *Z*-form (see the Supporting Information). (Methanesulfonyl)triazole **1q** having a 2-thiophenyl group was smoothly converted to the aminoalkenylated product **3q** in 94% yield. When 4-*n*-butyl-1-tosyl-1,2,3-triazole was treated with **2a** in the presence of rhodium catalyst, the desired azulene **3r** was obtained in 40% yield. [(4-Cyclohexenyl)methanesulfonyl]triazole **1s** turned out to be compatible with the optimal reaction conditions, providing the desired azulene **3s** in 89% yield.

Guaiazulene (1,4-dimethyl-7-isopropylazulene) was then investigated in the *N*-sulfonylaminoalkenylation using various triazoles (Scheme 3). Under the optimal reaction conditions, guaiazulene (**2b**) was readily aminoalkenylated with 4-phenyl-1-tosyl-1,2,3-triazole (**1a**), producing exclusively (*Z*)-**4a** in 96% yield. The structure of (*Z*)-**4a** was unambiguously determined by X-ray crystallography and NOE (see the Supporting Information). Likewise, the reaction efficiency was not influenced by the electronic properties of the triazoles. Triazoles having methyl and chloro groups on the phenyl ring worked equally well in the reaction with guaiazulene to give the corresponding azulenes **4b** (96%) and **4c** (85%). 4-Aryl-1-mesyl-1,2,3-triazoles did not effect the reaction efficiency. Guaiazulene was subjected to 1-mesyl-4-phenyl-1,2,3-triazole, leading to the formation of **4d** in 93% yield. The aminoalkenylation of guaiazulene proceeded

Scheme 3. Aminoalkenylation of Guaiazulenes[a]

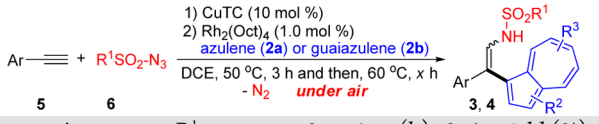


[a]**1** (0.2 mmol) and **2b** (0.3 mmol) in the presence of $Rh_2(Oct)_4$ (1.0 mol %) were heated in DCE (1.0 mL) at 60 °C for 2−6 h under air.

exclusively with 2-thiophenyl-substituted triazoles to deliver (*Z*)-**4e** (89%). Although 4-*n*-butyl-1-tosyl-1,2,3-triazole (**1r**) gave the desired product **4f** in low yield (43%), cyclohexenyl-substituted triazole (**1s**) was subjected to **2b** in the presence of rhodium catalyst, producing (*Z*)-**4g** in 87% yield.

To demonstrate the synthetic practicability of this *N*-sulfonylaminoalkenylation, we next conducted a three-component one-pot synthesis of the azulene derivatives (**3** and **4**) starting from terminal alkynes **5**, *N*-sulfonyl azides **6**, and azulene **2a** or guaiazulene **2b** (Table 2).[8] Although the aminoalkenylated product **3a** was produced from phenylacetylene, tosyl azide, and azulene in the presence of copper(I) thiophene-2-carboxylate (CuTC) and $Rh_2(Oct)_4$ in DCE, it was slowly decomposed depending on reaction time under the optimal reaction

Table 2. Aminoalkenylation in a Semi-One-Pot Process[a]



entry	Ar	R^1	2	time (h)	3, 4	yield (%)
1	Ph	4-Me-C_6H_4	**2a**	2	**3a**	73 (10:1)
2	3-Me-C_6H_4	4-Me-C_6H_4	**2a**	4	**3h**	74 (10:1)
3	4-Me-C_6H_4	4-Me-C_6H_4	**2a**	4	**3i**	67 (10:1)
4	4-MeO-C_6H_4	4-Me-C_6H_4	**2a**	3	**3j**	65 (10:1)
5	3-Cl-C_6H_4	4-Me-C_6H_4	**2a**	10	**3l**	56 (10:1)
6	4-CF_3-C_6H_4	4-Me-C_6H_4	**2a**	10	**3o**	78 (20:1)
7	Ph	CH_3	**2a**	4	**3b**	76 (10:1)
8	Ph	4-Me-C_6H_4	**2b**	4	**4a**	82 (*Z*)
9	4-Me-C_6H_4	4-Me-C_6H_4	**2b**	4	**4b**	83 (*Z*)
10	4-Cl-C_6H_4	4-Me-C_6H_4	**2b**	3	**4c**	63 (*Z*)
11	Ph	CH_3	**2b**	6	**4d**	84 (*Z*)

[a]Reactions were carried out in a semi-one-pot process (see the Supporting Information for detailed procedures). Ratios in parentheses are *Z*/*E* ratios.

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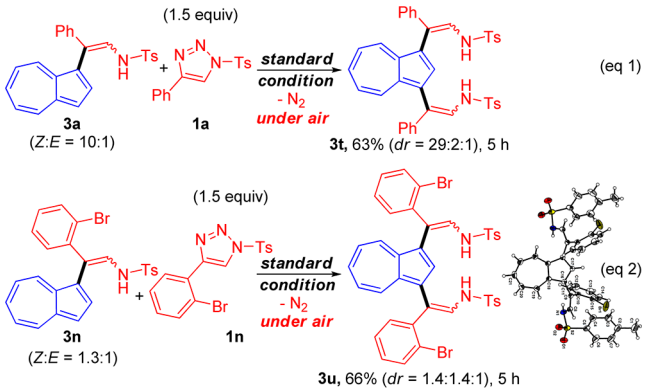
conditions. As a control experiment, when the azulene **3a** was treated with CuTC, it was decomposed without isolable compounds, indicating that azulene is sensitive to Cu catalyst. Thus, we attempted synthesis of the azulene derivatives (**3** and **4**) via a three-component semi-one-pot method. Phenylacetylene **5a** (0.20 mmol) and tosyl azide **6a** (0.22 mmol) in the presence of CuTC (10 mol %) in DCE (1 mL) were placed in a reaction vessel, and the reaction mixture was stirred at 50 °C. After disappearance of both **5a** and **6a** on TLC for 3 h at room temperature, the reaction mixture, including a newly prepared *N*-tosyltriazole, was filtered via a short pad of silica and used as the crude product in the following Rh-catalyzed *N*-sulfonylaminoalkenylation with azulene to produce **3a** in 73% (*Z*/*E* = 10:1) yield (entry 1). The three-component semi-one-pot method worked equally well with aromatic acetylene having 3-methyl, 4-methyl, 4-methoxy, 3-chloro, and 4-trifluoromethyl groups on the phenyl ring, producing a wide range of *N*-sulfonylaminoalkenylated azulenes (**3h**–**o**) in yields ranging from 56% to 78% (entries 2–6). We were pleased to obtain guaiazulene derivatives (**4a**–**c**) in good to excellent yields using guaiazulene (**2b**) and *N*-tosyltriazole (**1a**) generated in situ from terminal aromatic alkyne and tosyl azide **6a** (entries 8–10). *N*-Mesyltriazole generated in situ from alkyne and mesyl azide **6b** turned out to be compatible with the reaction conditions, producing **3b** and **4d** in good yields (entries 7 and 11).

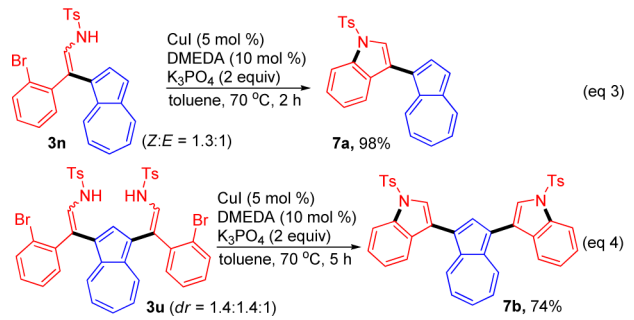
Next, second *N*-sulfonylaminoalkenylation of **3** obtained from triazole **1** and azulene **2** was attempted. When **3a** was again treated with **1a** (1.5 equiv) under the optimal reaction conditions, the desired compound **3t** was produced in 63% yield (eq 1). *N*-Sulfonylaminoalkenylated **3n** was also subjected



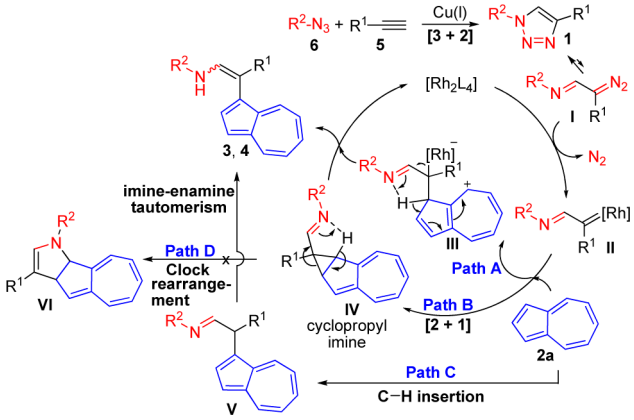
to triazole **1n** to provide **3u** in 66% yield. The structure of (*Z*,*Z*)-**3u** was unambiguously determined by X-ray crystallography (eq 2, see the Supporting Information).

To our delight, when azulene **3n** (*Z*/*E* = 1.3:1) having a 2-bromophenyl-substituted enamine moiety was treated with CuI (5 mol %), DMEDA (10 mol %), and K_3PO_4 (2 equiv) in toluene at 70 °C for 2 h, the cross-coupling product, 3-(azulen-1-yl)indole (**7a**), was obtained in quantitative yield (eq 3).[9] This result indicates that isomerization of the enamine double bond in **3n** easily occurred during the coupling reaction. Employment of this intramolecular cross-coupling reaction to 1,3-bis(*N*-sulfonylamino)alkenyl-substituted azulene **3u** provided 1,3-bis(indolin-3-yl)azulene **7b** in 74% yield (eq 4).

A plausible mechanism for the *N*-sulfonylaminoalkenylation of azulene derivatives is described in Scheme 4. First, a reversible ring–chain tautomerization of *N*-sulfonyl-1,2,3-triazole **1** provides α-diazo imine **I**.[10] The sequential irreversible reaction of **I** with rhodium(II) affords α-imino rhodium(II) carbenoid **II**



Scheme 4. Plausible Mechanism



together with liberation of molecular nitrogen. Nucleophilic addition of azulene **2a** to the electrophilic carbene center of **II** affords the rhodium-bound zwitterionic intermediate **III** (path A). Then, anionic rhodium of **III** releases an electron pair, which moves into the imine moiety to make the nitrogen atom basic enough to abstract an allylic proton to provide the (*N*-sulfonylamino)alkenylated azulene (**3** and **4**) with regeneration of the rhodium(II) catalyst. Alternatively, [2 + 1] cycloaddition of α-imino carbene **II** to 1,2-olefin in a five-membered ring of azulene **2a** could give rise to the cyclopropylimine **IV**. After that, intramolecular proton transfer of **IV** furnishes the *N*-sulfonylaminoalkenylated azulene (path B). Another plausible mechanism is that the concerted directed insertion of **II** into a C–H bond of azulene would lead to the formation of **V**, which upon imine–enamine tautomerization affords **3** and **4** (path C). However, because the cyclopropyl imine **IV** and imine-substituted azulene **V** were not observed in NMR studies in DCE-d_4, paths B and C are ruled out in the catalytic cycle at the present stage (see the Supporting Information). There is no formation of **VI** via Clock rearrangement of cyclopropyl imine **IV** (path D). The elucidation of the detailed mechanism of the *N*-sulfonyl aminoalkenylation of azulene derivatives must wait further study.

In conclusion, we have reported an efficient rhodium-catalyzed diastereoselective *N*-sulfonylaminoalkenylation of azulenes with *N*-sulfonyl-1,2,3-azides, producing a myriad of aminoalkenylated azulenes together with N_2 as the single byproduct. This procedure can be successfully applied to rhodium-catalyzed diastereoselective *N*-sulfonylaminoalkenylation of azulene derivatives starting from terminal alkynes and *N*-sulfonylazides through a three-component semi-one-pot process.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray crystallographic data for **3u** and **4a** (CIF), and ^{1}H, ^{13}C NMR, and NOE spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: phlee@kangwon.ac.kr.

Notes

The authors declare no competing financial interest.

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