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Reactivity of Arynes for Arene Dearomatization

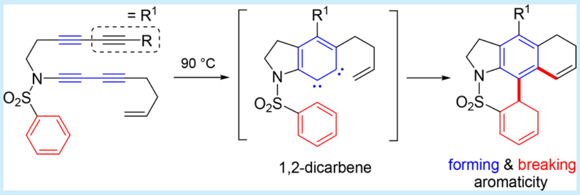
Rajdip Karmakar,[†] Anh Le,[†] Peipei Xie,[‡] Yuanzhi Xia,*[‡] and Daesung Lee*[†]

[†]Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, United States

[‡]College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang Province 325035, People's Republic of China

Supporting Information

ABSTRACT: An unprecedented aryne-mediated dearomatization reaction is described. An aryne intermediate generated from arenesulfonyl ynamide-tethered triynes and tetraynes reacts with both the π-systems of a tethered alkene and the arenesulfonyl group to generate cyclohexa-1,3-diene-containing pentacyclic and hexacyclic frameworks. Density functional theory (DFT) calculations show a nucleophilic dearomatization mechanism involving a zwitterionic intermediate derived from an aryne. A novel halogen effect on the efficiency of the dearomatization and deterrence of aromatization of the cyclohexa-1,3-diene moiety was also observed.



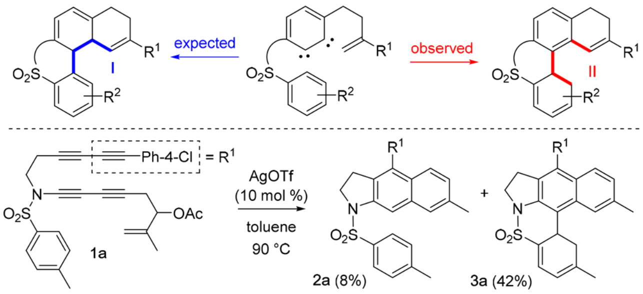
The reactivity of arynes is generally manifested as a strained alkyne, 1,2-diradical, or 1,2-zwitterion, depending on the reacting counterpart.[1] In the presence of π-philic transition metals, arynes participate in C−H insertion, which is evidence for the involvement of the 1,2-dicarbenoid.[2] Although arynes can potentially behave as a 1,2-dicarbene, this reactivity has never been revealed in any aryne-mediate transformations. The arene-dearomatization reaction described herein is the first evidence that the aryne species can interact with two π-systems through free 1,2-dicarbene reactivity.[3]

Dearomatization of arenes to cyclohexa-1,3- or cyclohexa-1,4-dienes could be achieved under a variety of conditions.[4] Among these, breaking aromaticity by adding a nucleophile onto arenes is limited to only a small range of arene structures.[4p−r] Different from polycyclic arenes,[5] monocyclic arenes react only under harsh conditions, resulting in low yield,[4r,6] unless complexed with certain transition metals.[4q,s,7] In this regard, the facile dearomatization of benzene via Diels−Alder reaction with aryne is unique,[8] wherein the relief of strain energy of arynes[9] should play a crucial role.

In light of the previously reported Ag(I)-catalyzed C−H insertion reaction,[2] we surmised that, in an appropriate environment, the 1,2-dicarbenoid can participate in two independent C(sp^2)−H insertion events (see Scheme 1). When **1a** was subjected to typical conditions (10 mol % AgOTf, toluene, 90 °C),[10] two products **2a** and **3a** were obtained.[11] While **2a** is the result of a mono C−H insertion, followed by the elimination of AcOH, the product **3a** can be considered as the result of an unprecedented 1,2-dicarbene mechanism.

Based on the formation of novel multicyclic framework involving arene dearomatization, we further explored the scope of this transformation. First, we tried to optimize the reaction conditions, along with the variation in the structure of the tethered alkene (see Table 1). It was found that AgOTf did not have a noticeable effect on the reaction, and $PhCF_3$ was the most favorable solvent (entry 1). The substituent on the alkene tether, for example, p-nitrophenylcarboxy and pivaloxy group at the allylic position has almost no effect on yields (entry 2 vs entry 3). Relocating the oxygen substituent from the allylic to the propargylic position did not affect the yield (entry 4 vs entry 5). Free hydroxyl group such as in **1f** did not interfere with the reaction,[12] affording **3e** in comparable yield (entry 6). Substrate **1g**, containing a styryl moiety, produced hexacyclic product **3g** (entry 7), whereas a similar substrate **1h** afforded product **4h** and **2h** in 40% and 18% yields, respectively (entry 8).

Scheme 1. Discovery of Aryne-Mediated Dearomatization



At this juncture, we surmised that the yield of the reaction could be improved by circumventing the elimination process, thus, we explored the reactivity of tetraynes devoid of an oxygen substituent (see Table 2). Tetrayne **1i** containing a carboxylate in the tether afforded **4i** with a 1.3:1 diastereomeric ratio (entry 1). Tetrayne **1j** containing an allyldimethylsilyl group afforded silacyclic product **4j** in 35% yield (entry 2). Although not involving the elimination step, the yield of **4i** and **4j** still remained in a marginal range. A

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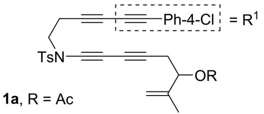
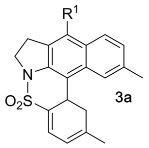
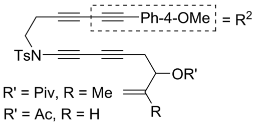
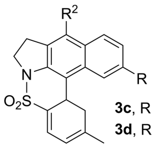
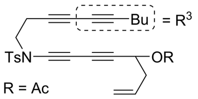
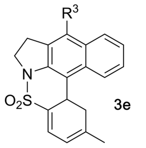
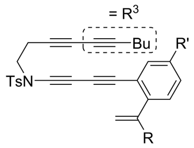
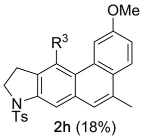
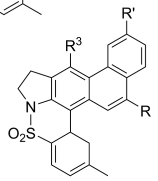
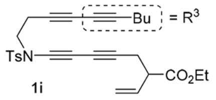
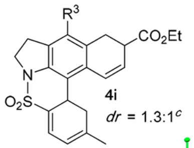
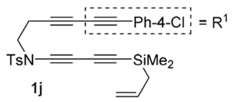
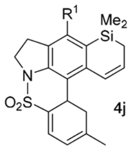
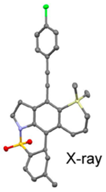
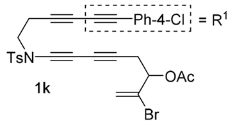
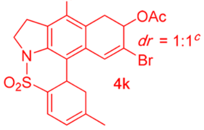
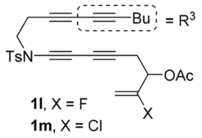
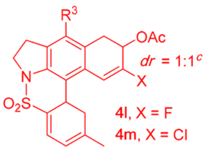
Table 1. Optimization and the Effect of an Alkene Tether

entry	substrate	conditions^{a}	product	yield (%)^{b}
		A	 3a	42^{c}
		B		35^{c}
1	**1a**, R = Ac	C		44^{c}
2	**1b**, R = 4-NO$_2$-Benzoyl	A		47^{d}
				
3	**1c**, R' = Piv, R = Me	A	**3c**, R = Me	45
4	**1d**, R' = Ac, R = H	A	**3d**, R = H	40^{e}
			 3e	
5	**1e**, R = Ac	C		40
6	**1f**, R = H	C		41
			 2h (18%) 	
7	**1g**, R = H, R' = H	B	**3g**, R = H, R' = H	36
8	**1h**, R = Me, R' = OMe	C	**3h**, R = Me, R' = OMe	40

^{a}Conditions: **A** = AgOTf (10 mol %), PhCH$_3$, 90 °C; **B** = PhCH$_3$, 90 °C; **C** = PhCF$_3$, 90 °C. ^{b}Isolated yield. ^{c}Yield from **1a**. ^{d}Yield from **1b**. ^{e}In PhCl and 1,2-dichloroethane, **3d** was obtained in 34% and 40% yields, respectively.

Table 2. Effect of the Substituents on the Alkene

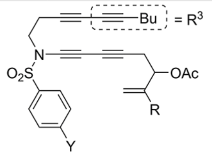
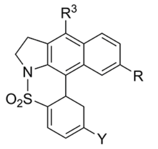
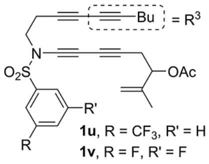
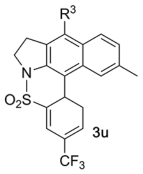
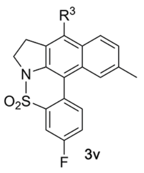
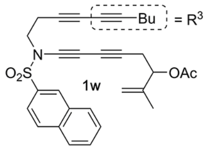
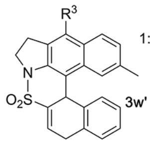
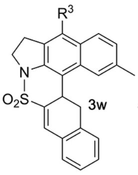
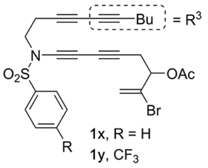
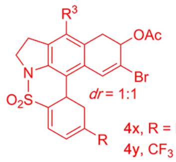
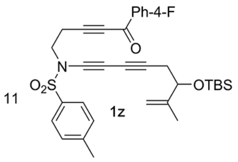
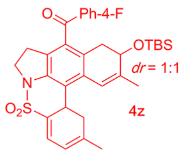
entry	substrate	conditions^{a}	product	yield (%)^{b}
1	 **1i**	B	 **4i** *dr* = 1.3:1^{c}	38
2	 **1j**	C	 **4j**  X-ray	35^{d}
3	 **1k**	C	 **4k**	67
				
4	**1l**, X = F	C	**4l**, X = F	72
5	**1m**, X = Cl	C	**4m**, X = Cl	61
6	**1n**, X = Br	C	**4n**, X = Br	63
7	**1o**, X = I	C	**4o**, X = I	67

^{a}Conditions: **B** = PhCH$_3$, 90 °C; **C** = PhCF$_3$, 90 °C. ^{b}Isolated yield. ^{c}Mixture of diastereomers. ^{d}Slightly higher 43% yield was obtained with a phenyl instead of a tolyl group.

significant increase in yield was achieved by installing a vinyl bromide moiety in tetrayne **1k**, which yielded **4k** in 67% yield (entry 3). Encouraged by this result, the impact of different halogen substituents on the efficiency of the reaction was examined. From tetraynes **1l**−**1o**, which differ only by the halogen substituent on the alkene moiety, pentacyclic products **4l**−**4o** were obtained in good yields (entries 4−7). One noteworthy observation is that the elimination of AcOH is shunted in these products containing a haloalkene moiety. The highest yield with **1l** bearing a fluoride-substituent might be the consequence of the carbocation-stabilizing effect of the fluoride with an intermediate along the reaction path.[13]

Next, we explored the impact of electron-donating and electron-withdrawing substituents on the arenesulfonamide (see Table 3). The reaction of **1p** containing a 4-MeOPh afforded only 37% yield of **3p** (entry 1), whereas **1q** with a phenyl group provided **3q** in 48% yield (entry 2). Substrate **1r** with a phenyl instead of a methyl group on the alkene afforded **3r** in 46% yield (entry 3). The 4-fluoro and 4-trifluoromethyl groups in **1s** and **1t** slightly improved the yield, providing **3s** and **3t** in 53% and 59% yields, respectively (entries 4 and 5). These examples clearly suggest that more electron-deficient arenesulfonyl groups can improve the yield. Substrate **1u** with 3-CF$_3$ afforded **3u** in 51% yield (entry 6), while **1o** with a 3,5-difluophenyl group provided **3v** in 35% yield (entry 7). Naphthalene-2-sulfonyl substrate **1w** furnished a 1:2.3 mixture of **3w′** and **3w** in 53% yield (entry 8).

Table 3. Effect of the Substituents on the Arenesulfonamide

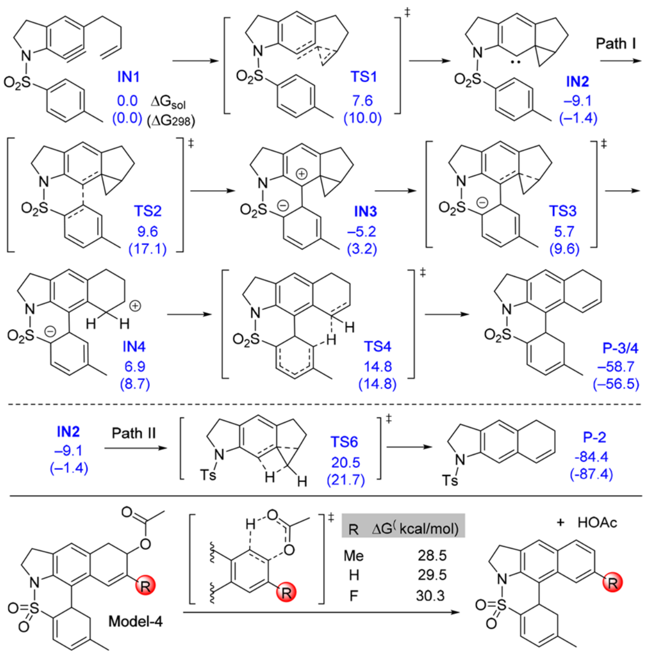
entry	substrate	product^{a}	yield (%)^{b}
			
1	**1p**, Y = OMe, R = Me	**3p**, Y = OMe, R = Me	37
2	**1q**, Y = H, R = Me	**3q**, Y = H, R = Me	48
3	**1r**, Y = H, R = Ph	**3r**, Y = H, R = Ph	46
4	**1s**, Y = F, R = Me	**3s**, Y = F, R = Me	53
5	**1t**, Y = CF$_3$, R = Me	**3t**, Y = CF$_3$, R = Me	59
		 3u  3v	
6	**1u**, R = CF$_3$, R' = H		51
7	**1v**, R = F, R' = F		35
8	 **1w**	 3w′ 1:2.3 +  3w	53
			
9	**1x**, R = H	**4x**, R = H	61
10	**1y**, CF$_3$	**4y**, CF$_3$	76^{c}
11	 **1z**	 **4z**	64^{d}

^{a}PhCF$_3$, 90 °C. ^{b}Isolated yield. ^{c}In a 1.0 g-scale reaction, **4y** was isolated in 67% yield. ^{d}PhCF$_3$, 120 °C.

Comparison of **1x** and **1y** containing a vinyl bromide clearly shows the beneficial effect of an electron-withdrawing 4-CF_3 on the arenesulfonyl moiety, providing 61% and 76% yield of **4x** and **4y**, respectively (entries 9 and 10). The dearomatization occurred with the aryne intermediate generated from ketone-containing triyne **1z** providing **4z** at slightly higher temperature, where the silyl ether remained unreacted.[10e]

The mechanism of this unprecedented aryne-mediated dearomatization process was explored by DFT calculation,[14] employing a structurally simplified aryne **IN1** (see Scheme 2).

Scheme 2. DFT-Based Mechanistic Study[a]

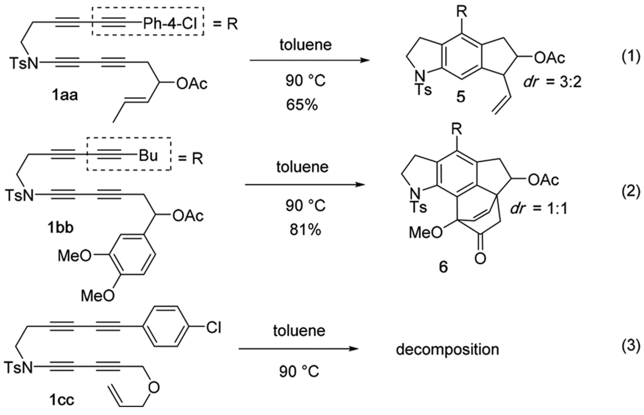


[a] ΔG_{sol} and ΔG_{298} are relative free energies (kcal/mol) calculated in solution and in the gas phase, respectively.

The calculated lowest energy pathway reveals a 1,2-dicarbene character of **IN2** through aryne, which promotes the concerted formation of a cyclopropyl carbene via a relatively low-energy transition state **TS1**. Carbene **IN2** behaves similar to a zwitterion, such that it undergoes nucleophilic addition (Path I) onto an electron-deficient arenesulfonyl group via **TS2** to generate 1,3-zwitterion **IN3**. The ring expansion of the cyclopropyl moiety of **IN3** generates isomeric 1,6-zwitterion **IN4**, which leads to the final product **P** via **TS4** for intramolecular proton transfer. The change of ΔG going from aryne **IN1** to product **P** is −58.7 kcal/mol, and the highest barrier involved in the dearomatization is only 14.8 kcal/mol; thus, this overall process should be kinetically and thermodynamically favorable. On the other hand, the energy of **TS6** leading to product **P-2** (Path II) is 10.9 kcal/mol higher than that of **TS2** leading to product **P-3/4**. Also, the unusual stability of the vinyl halide-containing products such as **4l**−**4o** toward aromatization was computationally studied. The DFT calculations with **Model-4** show that a fluoro-substituent raises the activation barrier for the AcOH elimination. Even though the calculations corroborate experimental observations, the reason for this unusual phenomenon is yet to be identified.

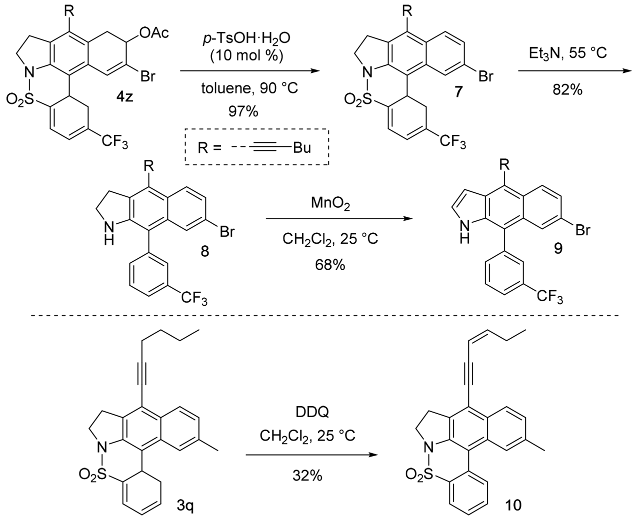
A limitation was noticed regarding the alkene structure on tetrayne substrates (see Scheme 3). A nonterminal alkene in **1aa** favorably participates in a type-I Alder-ene reaction, generating **8** (see eq 1 in Scheme 3). The electron-rich aromatic π-system in **1bb** led to only Diels−Alder reaction,[15] forming benzobarrelene **9** after hydrolysis (see eq 2 in Scheme 3), whereas allyl ether-tethered tetrayne **1cc** just decomposed (see eq 3 in Scheme 3). These results indicate that a terminal alkene tethered with a two-atom tether to the aryne moiety is required for dearomatization reaction.

Scheme 3. Substrates with an Unsuitable Alkene Moiety



The reactivity of a representative dearomatized compound **4z** was explored (see Scheme 4). Treatment of **4z** with *p*-TsOH·H_2O (10 mol %) at 90 °C induced aromatization via elimination of AcOH, affording compound **7**. The sulfonamide of **7** could be removed easily by treating **7** in Et_3N at 55 °C, providing compound **8**, which is the consequence of a base-mediated alkene isomerization and an E2-type elimination. The indoline moiety in **8** was oxidized by MnO_2 to generate a unique 1*H*-benzo[*f*]indole containing biaryl structure **9**. In contrast, oxidation of **3q** with DDQ afforded **10** with intact indoline moiety in low yield.

Scheme 4. Chemical Reactivity of Dearomatized Products



In conclusion, we discovered a novel dearomatization reaction mediated by the 1,2-dicarbene reactivity of arynes. In this process, one aromatic system is generated via HDDA reaction as a form of an aryne, the high reactivity of which then ensues the dearomatization of the tethered aryl group connected through a sulfonamide linkage. The efficiency of this transformation is profoundly affected by substrate structures, where a cation-stabilizing substituent on the tethered alkene and electron-withdrawing substituents on the arenesulfonyl group increased the efficiency of the reaction. DFT calculations revealed that the 1,2-dicarbene character of an aryne promoted cyclopropanation with the nearby alkene, followed by a nucleophilic attack of the remaining carbene as a form of zwitterion onto the electron-deficient arenesulfonyl group, leading to dearomatization after proton shift in the final step. The relatively strained pentacyclic framework can be readily converted to useful building blocks, including 1*H*-benzo[*f*]indole that contains a CF_3 group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01466.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1574874 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dsunglee@uic.edu.
*E-mail: xyz@wzu.edu.cn.

ORCID

Yuanzhi Xia: 0000-0003-2459-3296
Daesung Lee: 0000-0003-3958-5475

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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