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Communication

# Aryne 1,2,3,5-Tetrasubstitution Enabled by 3-Silylaryne and Allyl Sulfoxide via an Aromatic 1,3-Silyl Migration

Jiarong Shi,[§] Lianggui Li,[§] Chunhui Shan,[§] Junli Wang, Zhonghong Chen, Rongrong Gu, Jia He, Min Tan, Yu Lan,* and Yang Li*

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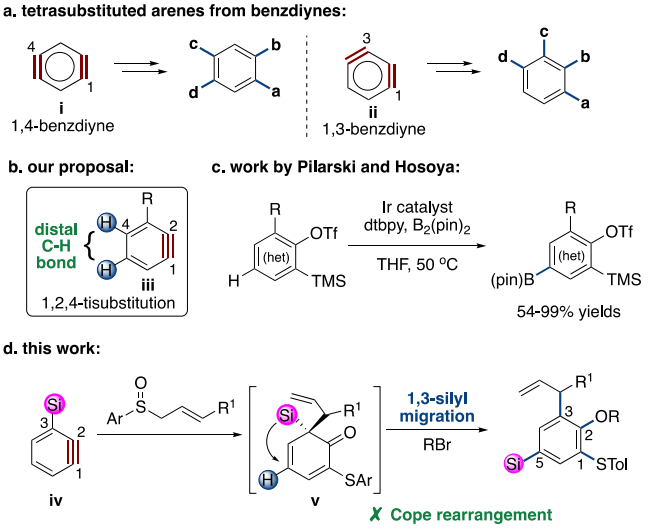
**ABSTRACT:** Although benzyne has been well-known to serve as a synthon that can conveniently prepare various 1,2-difunctionalized benzenes, the sites other than its formal triple bond remain silent in typical benzyne transformations. An unprecedented aryne 1,2,3,5-tetrasubstitution was realized from 3-silylbenzyne and aryl allyl sulfoxide, the mechanistic pathway of which includes a regioselective aryne insertion into the S═O bond, a [3,6]-sigmatropic rearrangement, and a thermal aromatic 1,3-silyl migration cascade.

As one of the most active organic intermediates, benzyne and its analogs have long been recognized as versatile benzene-based building blocks, which could expeditiously assemble numerous vicinal difunctionalized benzenes as well as benzofused compounds.[1] The formal triple bond character of benzyne, however, mechanistically prohibits the introduction of more than two substituents on the benzyne ring using conventional methods. This intrinsic restriction of benzyne has largely impeded its application in the preparation of polysubstituted benzenes. Although equivalents of benzdiyne[1o,2] and benztriyne[3] could be utilized, only limited reaction modes were reported along with lack of regioselective control in the cases of 1,4-benzdiyne **i** and 1,3-benzdiyne **ii** (Scheme 1a). Moreover, multistep preparation procedures for these "polyaryne" precursors also diminish the atom/step economy evaluation on this approach. An intriguing proposal is to utilize simple benzyne to realize polysubstitution tasks, which will require a selective C−H bond functionalization on the benzyne ring in a properly designed tandem or cascade process. Notably, the success of this strategy would not only break the restriction of benzyne 1,2-difunctionalization but also provide highly efficient and economical maneuvers toward polysubstituted benzenes.

Along with our study on aryne chemistry,[2a,c,e,g,h,k,4] we previously achieved a benzyne 1,2,3-trisubstitution protocol.[4b] Prompted by this work, we then aimed to reach the less accessible distal C−H bond of benzyne **iii**, where benzyne 1,2,4-trifunctionalization or more substitution could be conceived (Scheme 1b). To the best of our knowledge, however, there was no precedent on this type of transformation. In this context, the groups of Pilarski[5] and Hosoya[6] independently reported a Ir-catalyzed chemoselective C−H borylation reaction on *o*-silyl (hetero)aryl triflates, whereas the corresponding arynes were generated in a separate step (Scheme 1c). It can be envisioned that cascade benzyne polysubstitution processes containing a selective distal C−H bond functionalization would be more challenging. Herein, we wish to present our discovery on an unprecedented aromatic 1,3-silyl migration event via intermediate **v**, which was generated between 3-silylbenzyne **iv** and allyl sulfoxide (Scheme 1d). As a consequence of this thermal 1,3-silyl shift, a cascade process toward the expeditious construction of 1,2,3,5-tetrasubstitued arenes from single arynes was accomplished.

After searching for plausible solutions for benzyne 1,2,4-trisubstitution, we decided to use 3-silylbenzyne **iv** and allyl

**Scheme 1. Background and Our Work**

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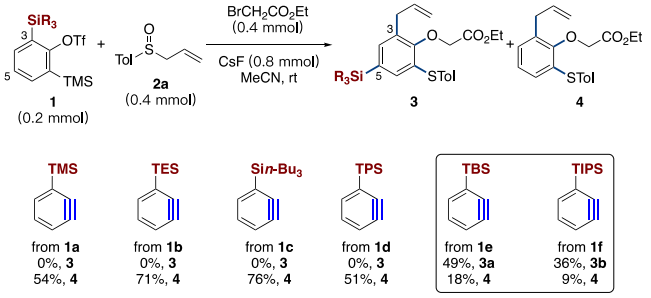
sulfoxide[4b] to examine this hypothesis (Scheme 1d). This design was based on the following considerations: (1) the 3-silyl group on benzyne is known to serve as an inductively electron-donating group (EDG)[7] that could direct the incoming sulfoxide oxygen to attack its *ortho*-position; (2) it might then act as a "blocking group" after the allyl group migrates to the C3-position and trigger a subsequent rearrangement, presumably a Cope rearrangement, on intermediate **v**.

As shown in Scheme 2, a series of 3-silylbenzyne precursors **1a**−**1f** were prepared, which could generate the corresponding

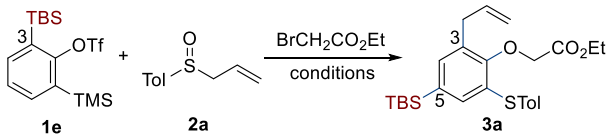
**Scheme 2. Reactions of 3-Silylbenzynes with Allyl Sulfoxide**




arynes upon activation with CsF in acetonitrile. These precursors were then subjected to the reaction with *p*-tolyl allyl sulfoxide (**2a**) and ethyl bromoacetate at room temperature. When **1a** with a 3-trimethylsilyl (3-TMS) group was used, the reaction only afforded a desilylation product **4** in 54% yield. By altering aryne precursors to **1b** with a 3-triethylsilyl (3-TES) group, **1c** with a 3-tri(*n*-butyl)silyl (3-*n*-$Bu_3Si$) group, or **1d** with a 3-triphenylsilyl (3-TPS) group, compound **4** remained the only obtained product. Intriguingly, when aryne precursors containing a 3-*tert*-butyldimethylsilyl (3-TBS) group (**1e**) and 3-tris(isopropyl)silyl (3-TIPS) group (**1f**) were examined, the main reaction path changed dramatically, affording **3a** and **3b** in 49% and 36% yields, respectively, along with certain amount of the desilylation product **4**. Notably, no product via Cope rearrangement was detected. Alternatively, the formation of **3a** and **3b** should proceed through a net 1,3-silyl migration on the benzene ring. In the presence of a fluoride ion, those silyl groups with less sterically hindered substituents are vulnerable, whereas both TBS and TIPS groups could sustain. Although the thermal 1,3-silyl shift of allylsilanes has been studied by Kwart[8] and Kira[9] and has attracted some theoretical attention,[10] harsh reaction conditions (>350 °C) for this transformation prohibited its synthetic application. Besides the much milder reaction temperature, our serendipitous discovery is of great interest, because, to the best of our knowledge, there was no precedent of thermal 1,3-silyl migration on aromatic systems. Moreover, this type of transformation provides a convenient means to deliver an aromatic silyl group to its *meta*-position specifically under certain circumstances.

With the above observation in hand, we decided to optimize the reaction conditions. As shown in Table 1, in the presence of ethyl bromoacetate, *p*-tolyl allyl sulfoxide (**2a**) could react with benzyne precursor **1e** to afford **3a**. By screening the reaction temperature (entries 1−3, Table 1), it was found that 50 °C was the best one. Altering the stoichiometry of CsF to 2.0 equiv gave only 50% of **3a** (entry 4). Additives, such as $Cs_2CO_3$ and 18-crown-6, were used but did not improve the

**Table 1. Reaction Optimization of 1,3-Silyl Migration**[a]




| entry | "F" (equiv) | additive (equiv) | solvent | temp (°C) | yield (%) |
|---|---|---|---|---|---|
| 1 | CsF (4.0) | no | MeCN | rt | 49 |
| **2** | **CsF (4.0)** | **no** | **MeCN** | **50** | **83** |
| 3 | CsF (4.0) | no | MeCN | 80 | 80 |
| 4 | CsF (2.0) | no | MeCN | 50 | 50 |
| 5 | CsF (4.0) | $Cs_2CO_3$ (2.0) | MeCN | 50 | 78 |
| 6 | CsF (4.0) | 18-c-6 (2.0) | MeCN | 50 | 29 |
| 7 | KF (4.0) | 18-c-6 (2.0) | MeCN | 50 | 41 |
| 8 | TBAF (4.0) | no | MeCN | 50 | 10 |
| 9 | CsF (4.0) | no | toluene | 100 | nr |
| 10 | CsF (4.0) | no | dioxane | 80 | trace |
| 11 | CsF (4.0) | no | THF | 50 | 64 |
| 12 | CsF (4.0) | no | DME | 50 | 68 |

[a]Conditions: **1e** (0.2 mmol), **2a** (0.4 mmol), "F", and $BrCH_2CO_2Et$ (0.4 mmol) in solvent (2 mL) overnight.

yield (entries 5 and 6). Other fluoride salts could not enhance the yield as well (entries 7 and 8). At last, different solvents were tested and all of them gave lower yields than that with MeCN (entries 9−12). Finally, the optimal conditions for this transformation were determined to be CsF in MeCN at 50 °C, furnishing **3a** in 83% yield with complete suppression of the desilylation pathway (entry 2).

We then explored the substrate scope for this transformation. As shown in Scheme 3, this reaction can be also scaled up to gram-scale, giving rise to **3a** in 79% yield. When 3-TIPS-substituted benzyne precursor **1f** was examined under the optimal conditions, **3b** was obtained in 60% yield. By altering ethyl bromoacetate to allyl bromide, cinnamyl bromide, and di-*tert*-butyl dicarbonate ($Boc_2O$), the corresponding products **3c**−**3e** were obtained as well. The employment of different aryl groups on sulfoxide afforded the desired products **3f**−**3j** in moderate to good yields. Sulfoxides with substituted allyl groups were tested, and products **3k**−**3p** were readily achieved. Among them, the X-ray crystallographic structure of **3k** unequivocally confirmed this 1,3-silyl migration event. Notably, desilylation reactions were suppressed, despite the fact that silyl groups are naturally vulnerable to the fluoride ion. We reasoned that the presence of either the *tert*-butyl group or triple isopropyl groups on silicon would kinetically disfavor the desilylation reaction. Consequently, the 1,3-silyl shift turned out to be the dominant path under the reaction conditions.

Distinctively, this cascade process still obeys the regioselective regulation when additional substituents are properly positioned on the benzyne ring, furnishing arenes with up to five substituents. For instance, when Kobayashi precursor **1g** was employed, pentasubstituted benzene **3q** was harvested in 56% yield (Scheme 4). Similarly, pentasubstituted benzenes **3r** and **3s** could be obtained in good yields as well from the corresponding aryne precursors **1h** and **1i**. The examples in Schemes 3 and 4 demonstrate that aromatic 1,3-silyl migration is a general scenario in this transformation, leading to an unprecedented tandem maneuver toward polysubstituted benzenes with substituents of different types.



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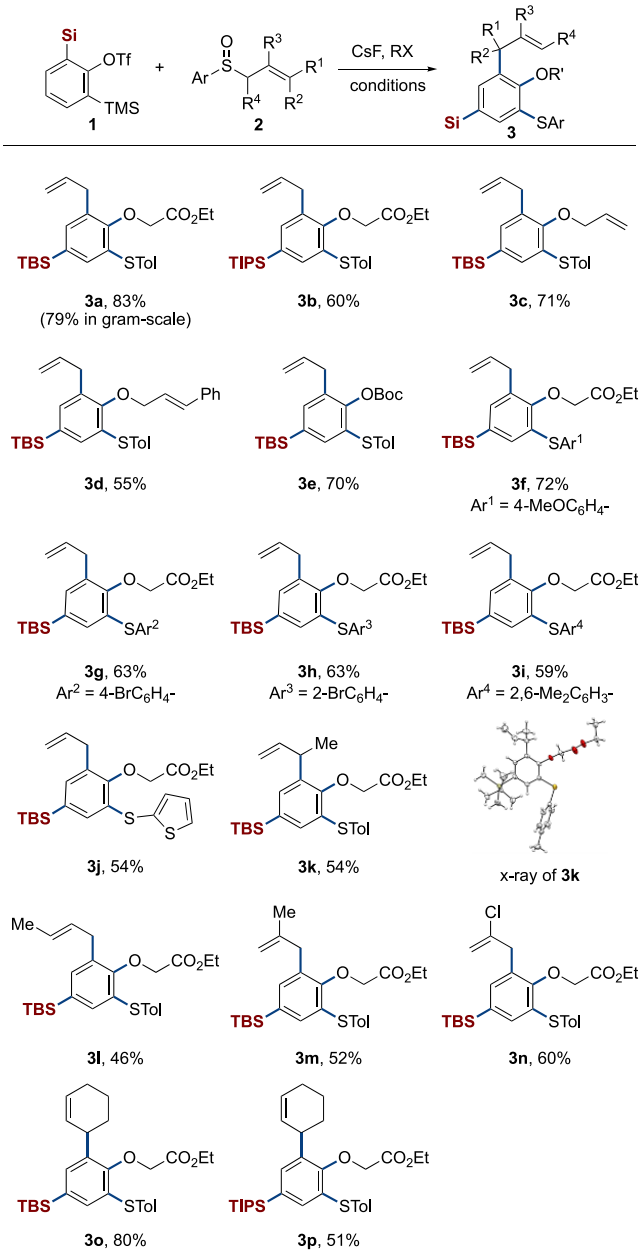
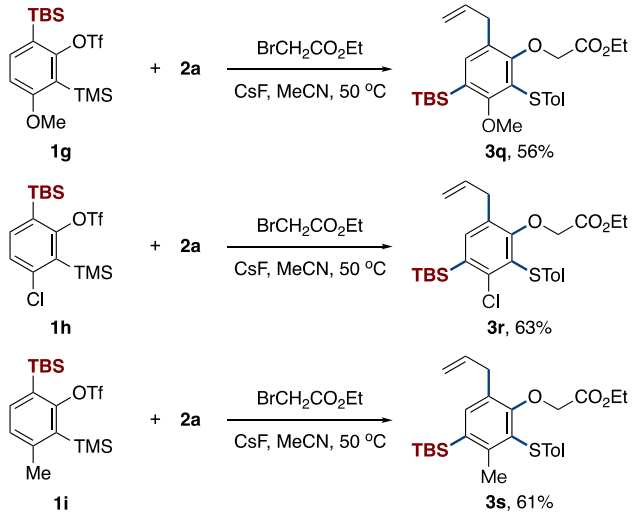
**Scheme 3. Substrate Scope**[a]

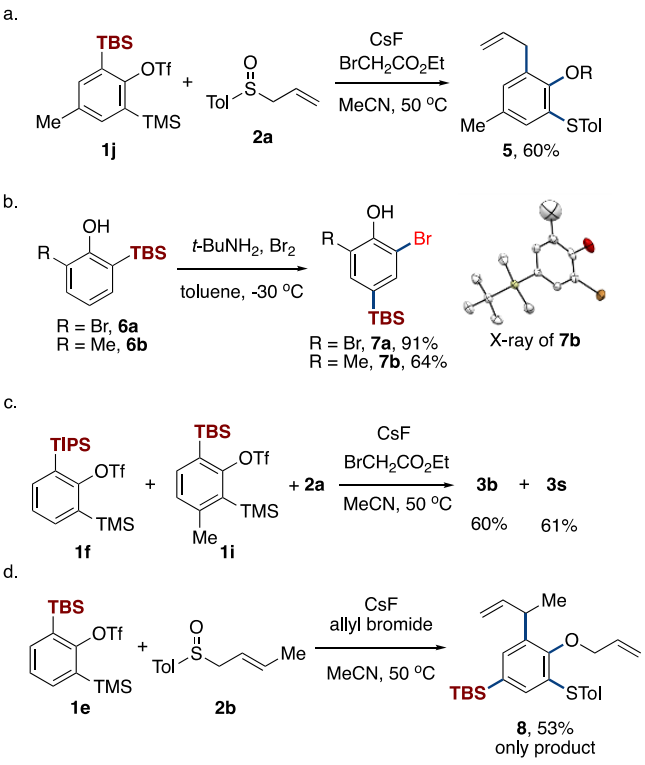



[a]Conditions: a mixture of **1** (0.2 mmol), **2** (0.4 mmol), RX (0.4 mmol), and CsF (0.8 mmol) in MeCN (2 mL) was heated at 50 °C overnight.

**Scheme 4. Pentasubstituted Benzenes**




**Scheme 5. Further Investigations**




Further studies were carried out in order to explore the scope and the mechanism of this transformation. When aryne precursor **1j** was employed, only desilylation product **5** was obtained in 60% yield, indicating that the 1,3-silyl shift can be prohibited by the presence of the C5-methyl group. To test the generality of aromatic silyl migration, 6-substituted 2-(*tert*-butyldimethylsilyl)phenols **6** were prepared (Scheme 5a). Under *ortho* bromination conditions ($Br_2$/*t*-$BuNH_2$ in toluene at −30 °C), the 1,3-silyl shift did happen after bromide adds to the C2-position, giving rise to products **7** (Scheme 5b). The X-ray crystallographic structure of **7b** was also determined. This observation suggests that aromatic 1,3-silyl migration could serve as a potentially useful tool under certain circumstances. To further understand the mechanistic aspect of this system, a crossover experiment was performed. When **1f** and **1i** were treated with **2a** under standard conditions, only **3b** and **3s** were obtained in 60% and 61% yields, respectively, supporting an intramolecular silyl migration pathway (Scheme 5c). Another experiment was then tested by using aryl crotyl sulfoxide **2b** and allyl bromide, which only afforded **8** in 53% yield (Scheme 5d). This result suggests a direct migration of the crotyl group to the *ortho* position of oxygen and phenolate allylation with allyl bromide should occur after crotyl migration.

Density functional theory calculations at the M06-2X level of theory were then performed. As shown in Scheme 6a, *in situ* generated 3-TBS-benzyne **vi** was chosen as the relative zero in calculated free energy profiles, which can react with aryl crotyl



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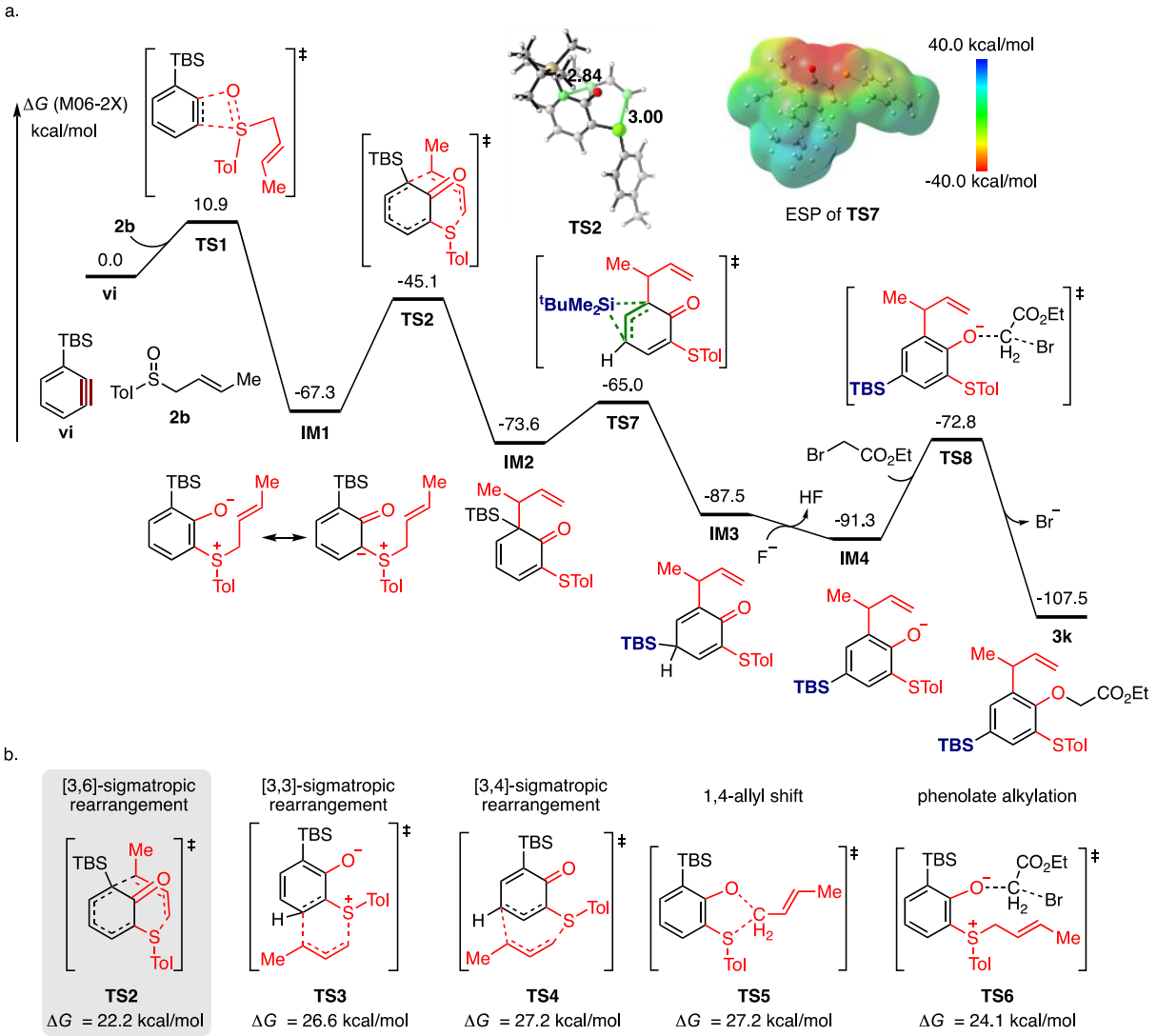
**Scheme 6. DFT Predicted Pathway between 3-TBS-benzyne vi and Crotyl Sulfoxide 2b**[a]




[a]The free energy values are calculated at the M06-2X level of theory in acetonitrile solvent.

sulfoxide **2b** via a four-membered metathesis-type transition state **TS1** to afford a zwitterionic sulfonium intermediate **IM1**. The calculated activation free energy for this step is only 10.9 kcal/mol, indicative of an easily reachable process. Intermediate **IM1** possesses a sulfonium ylide resonance structure as well. Consequently, a [3,6]-sigmatropic rearrangement can occur via transition state **TS2** with an energy barrier of 22.2 kcal/mol. The generated cyclohexadienone intermediate **IM2** is 6.3 kcal/mol more stable than **IM1**, which can be attributed by the cancelation of zwitterionic character on **IM1**. The geometry information on transition state **TS2** shows that the lengths of the forming C3−C(allyl) bond and the breaking S−C(allyl) bond are 2.84 and 3.00 Å, respectively, supportive of a concerted 10-electron sigmatropic rearrangement (Scheme 6a). In our theoretical study, several competitive pathways had also been examined at the **IM1** stage, such as [3,3]-sigmatropic rearrangement, [3,4]-sigmatropic rearrangement, allyl S → O shift, and phenolate alkylation (Scheme 6b). Those possibilities were excluded by their higher activation free energies via the corresponding transition states **TS3**−**TS6**. Although in our previous study an alternative pathway was proposed to account for the mechanism between benzyne and allyl sulfoxide,[4b] [3,6]-sigmatropic rearrangement turned out to be more likely to occur based on our calculations and experimental evidence in Scheme 5d.

After the formation of **IM2**, the silyl group was found to undergo a facile 1,3-migration via a four-membered ring transition state **TS7**, leading to the formation of a more stable intermediate **IM3**. In contrast, a plausible Cope rearrangement pathway at the **IM2** stage was precluded by its high activation energy of 23.0 kcal/mol (see the Supporting Information (SI) for details). After deprotonative aromatization on **IM3** and a subsequent alkylation on the generated phenolate **IM4** with ethyl bromoacetate via transition state **TS8**, product **3k** could be achieved. In this system, the electrostatic potential (ESP) surface of transition state **TS7** shows that the structure is highly charge-separated, where the positive charge (cool tones) is located on the silicon group and the center of the negative charge (warm tones) is on the oxygen atom (Scheme 6a). This charge-separation mechanism could be considered as a quasi-concerted process (see Figure S5 in the SI for detailed discussion), which is distinctly different from the previous theoretical studies on the 1,3-silyl shift of allylsilanes.[10] We speculated that the cationic silicon can be stabilized by one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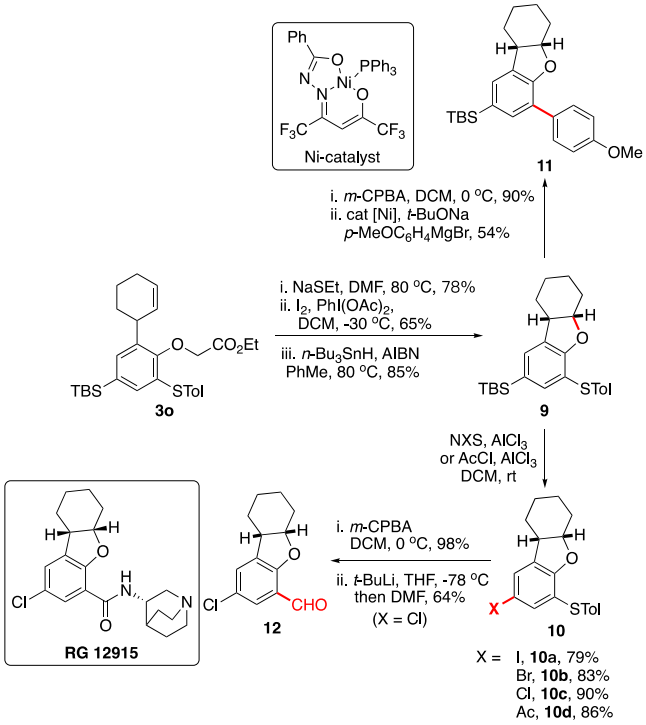
*tert*-butyl and two methyl groups and the anionic side forms an aromatic phenolate structure, which can be confirmed by a nucleus independent chemical shift (NICS) calculation (see Figure S6 in the SI).

We then investigated further manipulation on the products. As shown in Scheme 7, compound **3o** was chosen as an example. After deprotection and annulation, tricyclic compound **9** was obtained in three steps. The TBS group on compound **9** could then be converted to a variety of functional groups, such as iodo, bromo, chloro, and acetyl groups, to furnish **10a**–**10d**. Although a TBS group on benzene is normally difficult to replace, the electron-rich nature of the benzene ring on compound **9** accounts for its facile replacement by electrophilic species. Alternatively, the C–S bond on compound **9** was transformed to biphenyl **11** via a sequential oxidation and nickel-catalyzed cross-coupling reaction.[11] Moreover, the C–S bond on compound **10c** could be converted to benzaldehyde in two steps, giving rise to compound **12**. Notably, racemic compound **12** contains an identical core structure with that of bioactive molecule RG 12915, a potent antagonist of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor.[12]

In summary, we accomplished an unprecedented aryne 1,2,3,5-tetrasubstitution transformation between 3-silylaryne and allyl sulfoxides. This is the first example of single benzyne multifunctionalization involving a distal C–H bond functionalization cascade. In this study, a thermal aromatic 1,3-silyl migration was discovered, which possesses potential synthetic application under mild conditions. Moreover, our theoretical calculation clearly addressed the mechanistic aspects of this cascade transformation.

**Scheme 7. Synthetic Applications of 3o**




## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11119.

Experimental details for all chemical reactions and measurements and X-ray single crystallographic data (PDF)

### Accession Codes

CCDC 1923158 and 2033152 contain 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, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Yu Lan** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030; Green Catalysis Center, and College of Chemistry, Zhengzhou University, Zhengzhou, Henan 450001, P. R. China;* orcid.org/0000-0002-2328-0020; Email: lanyu@cqu.edu.cn

**Yang Li** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030;* orcid.org/0000-0002-0090-2894; Email: y.li@cqu.edu.cn

### Authors

**Jiarong Shi** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

**Lianggui Li** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

**Chunhui Shan** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030;* orcid.org/0000-0002-6175-1743

**Junli Wang** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

**Zhonghong Chen** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

**Rongrong Gu** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

**Jia He** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

**Min Tan** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. China 400030*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c11119


### Author Contributions

§J.S., L.L., and C.S. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

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