Communication

Cyclohexenynone Precursors: Preparation via Oxidative Dearomatization Strategy and Reactivity

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Cyclohexenynone Precursors: Preparation via Oxidative Dearomatization Strategy and Reactivity

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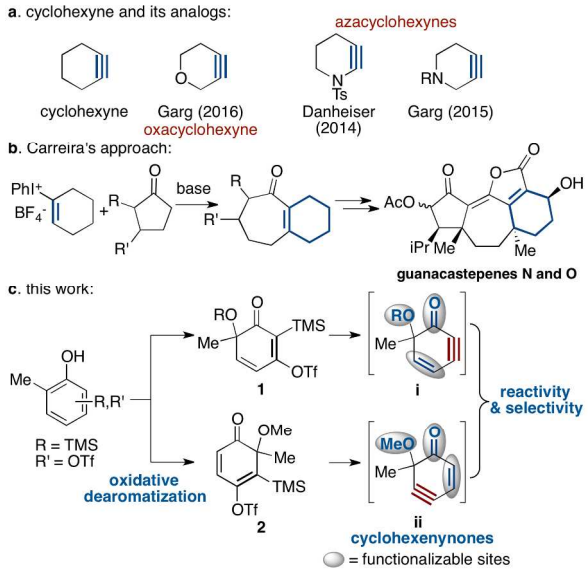
Supporting Information Placeholder

ABSTRACT: A unique approach towards the preparation of cyclohexenynone equivalents was successfully developed via oxidative dearomatization of aryne precursors, featuring multiple functionalities on the target rings. Upon activation, these *in situ* formed cyclohexenynone intermediates exhibit good to excellent reactivity with various trapping agents. Moreover, an unprecedented cascade was discovered with aryl allyl sulfoxides, revealing a deeper utilization of the alkyne bond by concomitantly introducing one nucleophile and two electrophiles.

Angle-strained cycloalkynes, in which the alkyne bond is embedded into size-restricted rings, belong to a group of reactive species that have been discovered and investigated since decades ago.[1] The most advantageous aspect of these species resides in their ease to concomitantly incorporate two functional groups on both alkyne carbons; whereas no other approaches could provide comparable solutions. Among them, benzyne gained tremendous accomplishments in recent years,[1a,2] primarily attributed to both the mild generation conditions developed by Kobayashi[3] and Hoye[4] and consequently their compatibility with diverse types of reactions. As the aliphatic variants of benzyne, either cyclohexyne or its heteroatom-embedded analogs (Scheme 1a), however, received much less attention,[1a,2b] despite the fact that they possess great potential as synthons in assembling multisubstituted cyclohexenes. The current underdeveloped situation of cyclohexyne chemistry can be partly attributed to the low synthetic efficiency associated with conventional generation methods, i.e. dehydrohalogenation,[5] in its early era.[1] Until recently, liberation of cyclohexyne analogs adopting Kobayashi's method from *o*-silyl triflate was successfully applied by the Guitian,[6] Garg,[7] and Danheiser[8] groups in a broad scope of transformations. In addition, both the Fujita-Okuyama[9] and Carreira[10] groups employed a 1,2-elimination on iodonium salt for the generation of cyclohexyne, which also led to an outstanding total synthesis of guanacastepenes N and O (Scheme 1b).[10b] Along with these studies, other methods were also reported by Banert[11] and Okano.[12] All these recent achievements unravel an exciting potential of hexatomic aliphatic cycloalkynes, whereas more remained unexplored and unexploited.

Beyond the triple-bond active site on a cyclohexyne, functionality on the other four positions can be equally essential, because multisubstituted cyclohexane structural motifs commonly exist in natural products, drugs, and bioactive molecules. Consequently, not only uncovering new reactivity of the alkyne bond itself, but also seeking for ready functionalizability of the other sites on the ring represent notable opportunities associated with the chemistry of cyclohexyne. Moreover, those additional functional groups might perturb both the physical property and chemical reactivity of a cyclohexyne intermediate. Comparing with those abundant arene substitution methods ranging from college textbooks to modern advanced synthesis,[13] unfortunately, ways to conveniently modify those unactivated sites on an aliphatic ring are rare. Therefore, it is of great interest to develop efficient means to incorporate various substituents/functional groups on the non-active sites of a cyclohexyne precursor in, preferentially, chemo- and regioselective manner so as to expand the realm of cyclohexyne.

Scheme 1. Background and our proposal

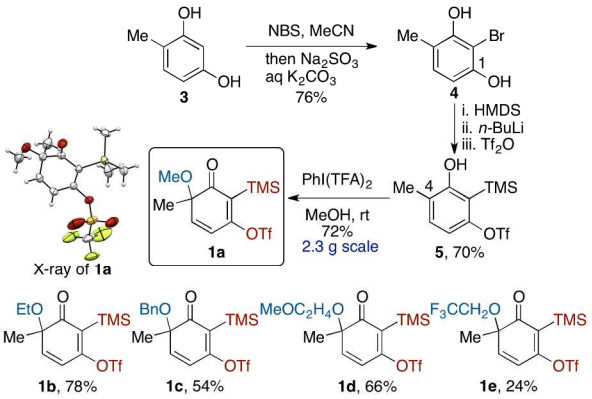


Along with our study on aryne transformations,[14] we recognized that both benzyne and cyclohexyne favor a common mild generation condition, namely Kobayashi's method. *Can we utilize readily functionalizable aryne precursors as building blocks in the preparation of multisubstituted cyclohexyne equivalents?* After searching for possible ways to reach this goal, we chose to pursue the oxidative dearomatization strategy of phenols with hypervalent iodine reagents,[15] which would allow the resulting aliphatic cycles to inherit those latent structural characters embedded in a benzene ring by means of unfolding its aromaticity. Here, we wish to present our study on a convenient preparation of cyclohexenynone precursors **1** and **2** via an oxidative dearomatization approach (Scheme 1c). Upon activation, they could generate the corresponding cyclohex-2-en-4-ynone **i** and cyclohex-4-en-2-ynone **ii**, respectively, which were found efficient cycloalkyne building blocks. In addition, a cascade transformation was also discovered with concomitant introduction of three substitu-

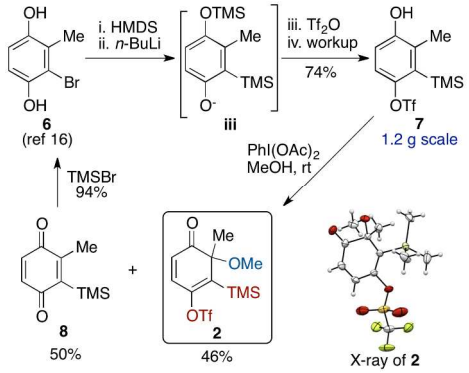
ents, namely one nucleophile and two electrophiles, onto the triple bond, revealing a new maneuver for cyclohexyne.

As shown in Scheme 2, the synthesis of **1** started from 4-methyl resorcinol (**3**). After bromination, 2-bromo-4-methyl resorcinol (**4**) was obtained in 76% yield. The formation of *o*-silyl phenyltriflate with selective conversion on C1-OH group was achieved in a one-pot process and gave rise to aryne precursor **5** in 70% overall yield, in which the TMS migration takes place exclusively from the sterically less congested C1 position on **4**. After optimization, the best dearomatization conditions for compound **5** was found to be $PhI(TFA)_2$ in methanol at room temperature, affording proposed compound **1a** in 72% yield over two gram-scale. In this step, the C4-position is the preferred site to accept the incoming methoxy group. Gratifyingly, both the TMS and OTf groups remain untouched under dearomatization conditions. Compound **1a** is a low-melting point pale-yellow solid, the X-ray crystallographic structure of which confirms the location of the OTf group. By employing the same protocol, products **1b-1e** could be readily achieved from **5** using different alcohols (Scheme 2).

Scheme 2. Synthesis of cyclohexenynone precursors 1



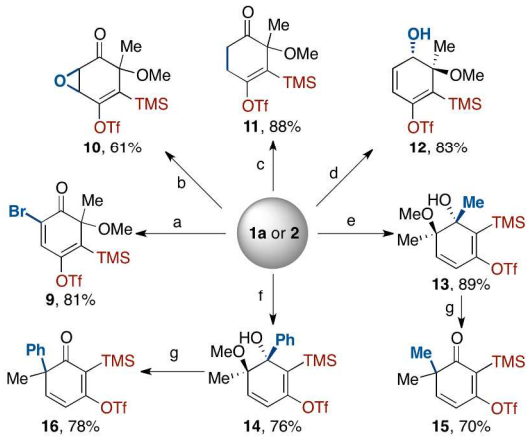
Scheme 3. Synthesis of cyclohexenynone precursor 2



Alternatively, in order to examine how the location of OH group affects dearomatization outcome as well as how the incorporated substituents behave during cyclohexyne reactions, compound **2** with a different pattern of functional groups was proposed (Scheme 3). The synthesis commenced with 2-bromo-3-methylbenzene-1,4-diol (**6**), the preparation of which has been reported by Ahmad (see the Supporting Information for detailed preparation).[16] Starting from compound **6**, the same one-pot protocol was employed to prepare **7** in 74% overall yield via intermediate **iii**. Oxidative dearomatization of **7** over gram-scale could afford **2** as a pale-yellow solid in 46% yield along with 50% of *p*-quinone **8**. Although the yield of **2** is not high, *p*-quinone **8** could be converted back to **6** with TMSBr in 94% yield,[17] giving rise to an overall good efficiency for this preparation procedure.

The presence of ketone, olefin, and alkoxy groups on **1** and **2** furnishes an opportunity to further expand the functional group diversity on these frameworks. As shown in Scheme 4, bromination of enone **2** with Br_2/Et_3N afforded compound **9** in 81% yield. Epoxidation of compound **2** took place selectively on unsubstituted olefin and gave rise to **10** in 61% yield. When compound **2** was treated with L-selectride, it was readily converted to **11** in 88% yield; whereas reduction of **2** with DIBAL-H afforded alcohol **12** in 83% yield. Moreover, alkylation with both MeLi and PhLi took place efficiently on compound **1a**, affording **13** and **14** in 89% and 76% yields, respectively. Notably, in the presence of $BF_3{\cdot}Et_2O$, both **13** and **14** readily underwent Pinacol-type rearrangement to produce **15** and **16**, respectively, with formation of quaternary carbon centers in highly selective manner. All these transformations not only unravel the versatile reactivity of olefin, ketone, and alkoxy moieties on **1** and **2**, but also exhibit that both the TMS and OTf groups are well-tolerated to a wide range of reaction conditions. Distinctively, the examples in Scheme 4 reinforce the value of our dearomatization-cyclohexyne protocol, the reactivity of which toward [4+2] cycloaddition has been examined as well (see Scheme S1 in SI).

Scheme 4. Further elaboration of 1a and 2



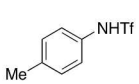
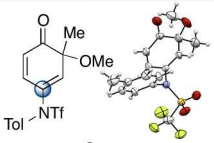
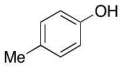
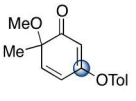
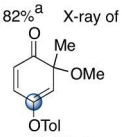
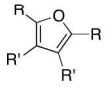
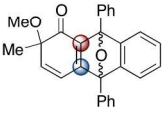
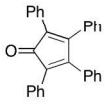
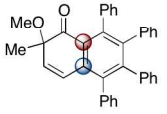
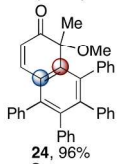
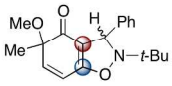
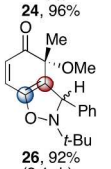
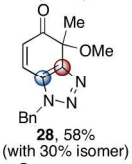
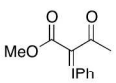
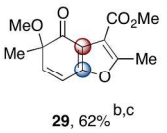
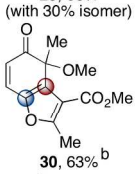
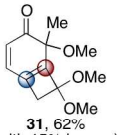
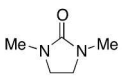
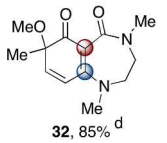
a) **2**, $Br_2/NaHCO_3$; b) **2**, H_2O_2-K_2CO_3, MeOH; c) **2**, L-selectride, THF; d) **2**, DIBAL-H, THF; e) **1a**, MeLi, Et_2O; f) **1a**, PhLi, Et_2O; g) $BF_3{\cdot}Et_2O$, MeCN, -78°C-rt

With both compounds **1** and **2** in hand, we decided to examine their potential applications as cyclohexenynone synthons and study their reaction behavior with different trapping agents. At the moment, we were aware of the possibility that the presence of additional groups on the ring might perturb the consequent cyclohexyne reactions in ways of the stability, reactivity, and selectivity of these highly active intermediate. Satisfyingly, both **1a** and **2** were found efficient to generate cyclohexenynones in the presence of fluoride salts. As shown in Table 1, when trifluoromethanesulfonyl (Tf) group-protected aniline was used as nucleophile, both cyclohexenynone precursors could react to produce single products **17** and **18** in high yields (entry 1). Phenol was found to be a good nucleophile as well, and its reactions with **1a** and **2** afforded **19** and **20**, respectively, in good yields and excellent regioselectivity (entry 2).

Both **1a** and **2** were found efficient cyclohexenynone precursors in Diels-Alder reactions and produced compounds **21-24** in high to excellent yields (entries 3 and 4, Table 1). In addition, *N*-*tert*-butyl-*α*-phenylnitrone was found to be a distinct trapping agent to react with both **1a** and **2** in excellent regioselectivity, affording **25** and **26** in 79% and 92% yields, respectively (entry 5).[18] Because of the presence of two stereogenic centers on both **25** and **26**, they were produced as mixture of diastereoisomers. The reaction of **1a** with benzyl azide furnished **27** in 78% overall

yield as a mixture of regioisomers in a ratio of 4.6:1 (entry 6).[19] Meanwhile, the reaction of **2** with benzyl azide could produce **28** in 58% yield along with 30% of its regioisomer. The reactions of **1a** and **2** with 2-phenyliodonio-3-oxobutanoate gave rise to formal [3+2] cycloadducts **29** and **30** in good yields, both of which were obtained as a single isomer (entry 7).[20] The reaction of 1,1-dimethoxyethene with **1a** did not lead to an observable amount of the desired product. Satisfyingly, [2+2] cycloaddition of **2** with 1,1-dimethoxyethene generated **31** in 62% yield along with 15% of regioisomer (entry 8).[21] Last, the reaction of 1,3-dimethyl-2-imidazolidinone (DMI) with **1a** afforded **32** in 85% yield with the formation of a [6,7]-fused ring system; whereas no desired product was detected from the same reaction with **2** (entry 9).

Table 1. Reactions of cyclohexenynone precursors 1a and 2

entry	trapping agent	reaction with **1a**	reaction with **2**
1		 **17**, 80%[a]	 **18**, 82%[a] X-ray of **18**
2		 **19**, 69%	 **20**, 75%
3		 **21**, 72% (1.4:1 dr)	 **22**, 87%[b] (2:1 dr)
4		 **23**, 73%	 **24**, 96%
5		 **25**, 79% (1.2:1 dr)	 **26**, 92% (2:1 dr)
6		 **27**, 64% (with 14% isomer)	 **28**, 58% (with 30% isomer)
7		 **29**, 62%[b,c]	 **30**, 63%[b]
8		no desired product	 **31**, 62% (with 15% isomer)
9		 **32**, 85%[d]	no desired product

Conditions unless otherwise stated are slow addition of **1a** or **2** (0.3 mmol) in MeCN (5 mL) via a syringe pump over 8 hours to a suspension of trapping agent (0.6 mmol) and CsF (0.6 mmol) in MeCN (5 mL) at room temperature. [a]CsF (0.9 mmol) was used; [b]1.5 mmol of trapping agent was used; [c]KF (0.6 mmol) and 18-c-6 (0.3 mmol) in THF (5 mL) was used instead of CsF in MeCN; [d]6 mmol of DMI was used.

Figure 1 gives the geometry optimizations of both cyclohexenynones **i** and **ii** using DFT calculations (B3LYP/6-31G(d)), expectedly generated from their corresponding precursors **1a** and **2**, respectively. Inspired by the Garg-Houk's distortion-interaction models for both arynes[22] and cyclohexynes,[7] we wondered whether the calculated structures of cyclohexenynones **i** and **ii** can explain their reaction selectivity. As shown in Figure 1, the optimized structure of cyclohex-2-en-4-ynone **i** indicates that internal angle x (134.7°) is significantly larger than angle y (121.9°), suggesting that the C1-position of intermediate **i** is more electrophilic. This computational prediction on regioselectivity is consistent with our experimental observation on **1a** (Table 1), which can be reasoned by the electron-withdrawing effect of the carbonyl group on cyclohexenynone **i**. In contrast, the calculated cyclohex-4-en-2-ynone **ii** shows that the difference between internal angles x (128.0°) and y (128.8°) is not distinct enough to ensure high regioselectivity. This is the consequence of competing electron-withdrawing effects on two terminals of the alkyne group, which counteracts one another. Gratifyingly, steric repulsion appears to be a dominant tuning factor on cyclohexenynone **ii**, furnishing good to high selectivity with other trapping agents (Table 1).

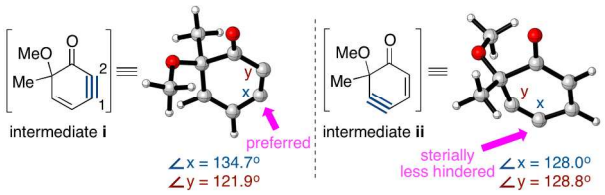
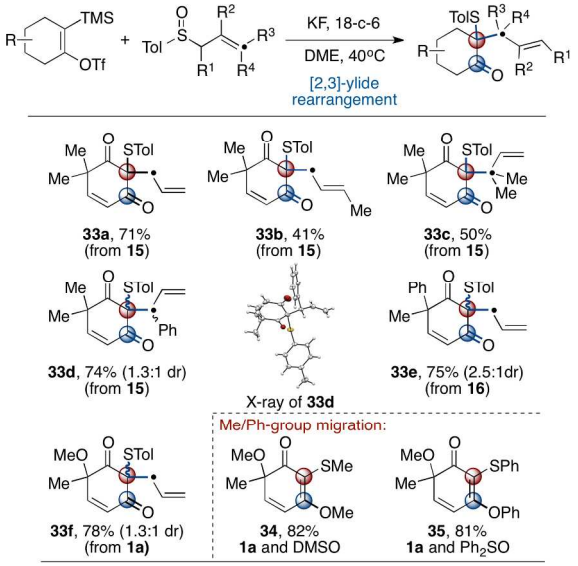


Figure 1. DFT calculations (B3LYP/6-31G(d)) of cyclohexenynones **i** and **ii** with the PCM solvent model for MeCN.

Scheme 5. Reactions with sulfoxides



Along with our study, we noticed that the immediate products from traditional cyclohexyne are olefins, which are intrinsically different from those embedded in aromatic systems after aryne reactions. This might offer us a chance to further elaborate the resulting nonaromatic olefin in designed cascade processes. As shown in Scheme 5, when compound **15** was treated with *p*-tolyl

allyl sulfoxide, compound **33a** was obtained in 71% yield (see Table S1 in SI for detailed optimization conditions), the mechanistic pathway of which involves a [2,3]-sigmatropic rearrangement on allyl sulfonium ylide.[23,24] In addition, the reactions between **15** and various aryl allyl sulfoxides afforded 2,2-disubstituted 1,3-cyclohexadiones **33b-33d** in moderate to good yields. When compounds **16** and **1a** were employed, **33e** and **33f** could be obtained in high yields, both of which are a mixture of diastereoisomers.[25] To the best of our knowledge, it is the *first example* to incorporate three substituents on the alkyne bond of a cyclohexyne, namely one nucleophile and two electrophiles, through "onium" ylide,[23] allowing a thorough utilization of cyclohexyne. Moreover, both DMSO and sulfinyldibenzene could react with **1a** as well, affording **34** and **35** in 82% and 81% yields, respectively (Scheme 5). In the absence of allyl group on these sulfoxides, a direct Me/Ph-group migration took place from sulfur to oxygen.[24]

In summary, we proposed and accomplished an oxidative dearomatization protocol from aryne precursors to prepare two types of cyclohexenynone equivalents, both of which exhibited good to excellent cycloalkyne reactivity with diverse trapping agents. Moreover, all the alkene, ketone, and methoxy group on the ring could be manipulated prior to the formation of cyclohexenynone, further expanding the structural diversity of cyclohexenynone scaffolds. The establishment of this oxidative dearomatization protocol sets up a platform for in-depth investigation of cyclohexyne chemistry in the presence of various substituents as well as the discovery of new synthetic maneuvers. As an exhibition, aryl allyl sulfoxides were found to react with cyclohexenynones to concomitantly form C=O, C-S, and C-C bonds through a cascade process.

ASSOCIATED CONTENT

Supporting Information. Experimental details for all chemical reactions and measurements and X-ray single crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[†]Qiu, D. and Shi, J. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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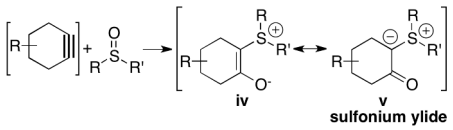

(25) In comparison, we tested the reaction between simple cyclohexyne precursor with *p*-tolyl allyl sulfoxide. Unexpectedly, no desired product was observed at all.

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