JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

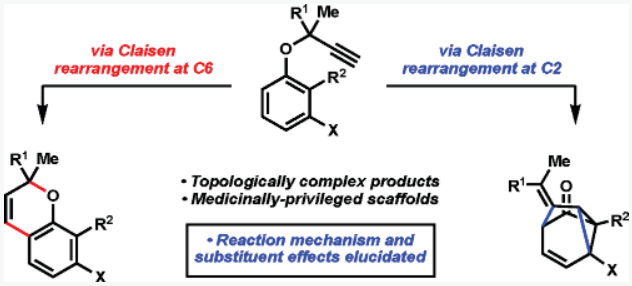
Computational and Further Experimental Explorations of the Competing Cascades Following Claisen Rearrangements of Aryl Propargyl Ethers: Substituent E ects on Reactivity and Regioselectivity

Melissa Ramirez Vito Vece Stephen Hanessian and K. N. Houk

Cite This: J Org Chem 2021 86 17955 17964 Read Online

CCESS | Metrics More | Article Recommendations | Supporting Information

ABSTRACT: We report a computational investigation of two reaction cascades occurring following the Claisen rearrangements of aryl propargyl ethers to the alternate *ortho* positions in unsymmetrical reactants. Our computations explain how substituents in uence reactivity and regioselectivity. Rearrangement to the substituted *ortho* carbon leads to a tricyclo[3.2.1.0]octane core, while rearrangement to an unsubstituted *ortho* carbon leads to a benzopyran. Density functional theory with B97X-D indicates that these reactions involve rate-determining Claisen rearrangements followed by subsequent reaction cascades of the Claisen rearrangement products depending on the presence or absence of a substituent at the *ortho* carbon.



INTRODUCTION

The Claisen rearrangement was first described in 1912 by the German chemist Rainer Ludwig Claisen (1851 1930) and has served as a valuable synthetic method in organic chemistry for over a century.[1 3] Variants of this classic reaction include [3,3]-sigmatropic shifts of allyl esters to give γ,δ-unsaturated carboxylic acid derivatives[4] and allyl ethers attached to diverse acyclic and cyclic core structures, including the aromatic Claisen rearrangement of aryl allyl ethers.[5 7] The aromatic Claisen rearrangement has been particularly useful in the context of *in vivo* biosynthetic transformations and toward the synthesis of natural products.[2a]

In 1962, Iwai and Ide reported an example of the aromatic Claisen rearrangement/electrocyclization reaction cascade of a 2-naphthyl propargyl ether in re uxing *N*,*N*-dimethylaniline leading to a 1,2-naphthopyran derivative.[8] Since then, Claisen cascades of aryl propargyl ethers have served as a means for accessing the benzopyran and benzofuran core structures of various natural products.[9,10] The mechanism of the reaction leading to benzopyran product was first proposed in 1968 by Zsindely and Schmid who demonstrated the intermediacy of an α-allenyl cyclohexanone.[11] This intermediate was proposed to undergo keto enol tautomerization, 1,5-hyrogen shift, and electrocyclization to provide the corresponding benzopyran product. Experimental and computational studies by Ishii[10c] and Lee,[15b] respectively, demonstrated that CsF promotes the aromatic Claisen rearrangement of aryl propargyl ethers leading to benzofuran analogs. Substituent and solvent effects on reactivity have also been explored experimentally.[12] While computational studies on regioselectivity in the Claisen rearrangement of aryl allyl ethers are well documented,[6,13] theoretical analysis of regioselectivity in the corresponding reaction of aryl propargyl ethers is limited. Instead, density functional theory (DFT) calculations have focused on elucidating the mechanism for reaction of aryl propargyl ethers **1** leading to benzofurans **2**[14] and benzopyrans **3** (Figure 1a).[15]

As part of their mechanistic study in support of the initial formation of an α-allenyl cyclohexadienone intermediate, Zsindely and Schmid subjected 2,6-dimethyl-1-phenyl propargyl ether **4** to a thermal cyclization (Figure 1b).[11] Although the presence of *ortho*-substituents in substrate **4** prevents access to benzopyran products, Zsindely and Schmid isolated bridged, tetracyclic cyclohexenone **5**, which harbors a fused cyclopropane ring (Figure 1b). The structure of cyclohexenone **5** was assigned spectroscopically. In the same report, reaction with propargyl ethers bearing various substitution patterns led to analogous bridged tetracycles. Based on this precedent, Trahanovsky and Mullen reported that the gas phase pyrolysis

Received: September 19, 2021
Published: November 30, 2021

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964

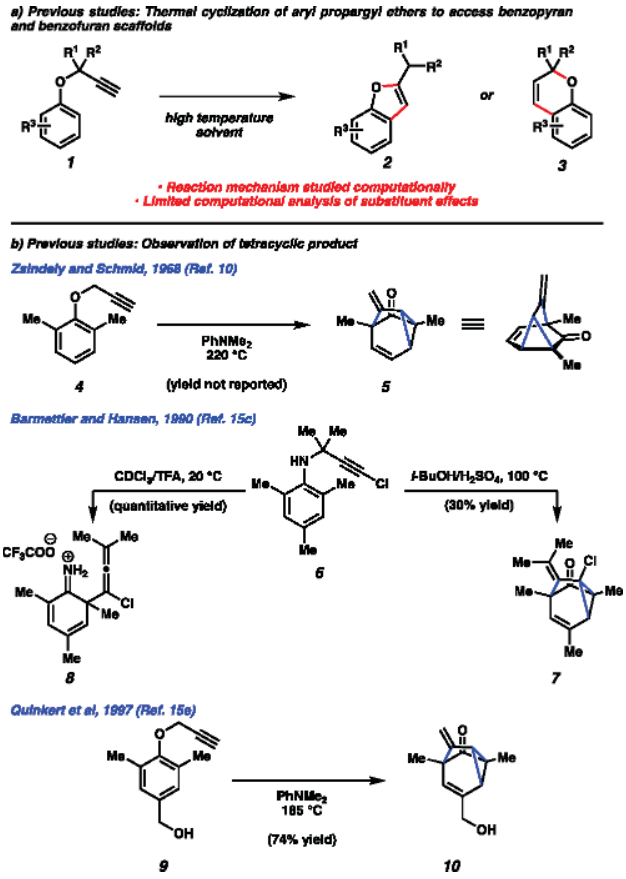


Figure 1. (a) Previous studies on the thermal cyclization of aryl propargyl ethers. (b) Previous observations of tetracyclic products.

of phenyl propargyl ether at 460 °C leads to a 2-allenyl cyclohexadienone species.[16a,b] The authors proposed that the cyclohexadienone intermediate subsequently undergoes a concerted and thermally allowed six-electron concerted reaction involving a bridged cyclopropane that is structurally similar to tetracycle **5**.

Barmettler and Hansen studied the Claisen rearrangement of *N*-protonated, *N*-propargyl substituted anilines under strong acidic conditions.[16c] As an example, the aniline derivative **6** led to the fused cyclopropane **7** in 30 yield (Figure 1b). Related examples of reactions with other *N*-propargyl substituted aniline derivatives also led to fused cyclopropanes in poor yields. Notably, racemic mixtures of these compounds could be separated by chiral HPLC. Finally, in 1997, Quinkert[16d] and co-workers performed the Claisen cascade with substrate **9** and obtained adduct **10** in 74 yield after distillation (Figure 1b).

Until recently, the synthetic utility of this remarkable transformation in accessing cyclopropane-containing, sp^3-rich carbocycles had remained untapped. In 2018, our group discovered its occurrence during the total synthesis of the yaequinolones J1 ans J2.[9] To our knowledge, reactivity in this transformation had not been explored with substrates aside from the biased systems presented by Zsindely,[11] Barmettler,[16c] and Quinkert[16d] (Figure 1b). Nonetheless, nature has long produced architecturally complex molecules bearing the tricyclo[3.2.1.0]octane scaffold, as demonstrated by the natural products shown in Figure 2. Elegantly conceived insights into the biogenesis of polysubstituted diterpenes such as ishwarane (**12**) and trachylobane (**13**) were first proposed by Wenkert in

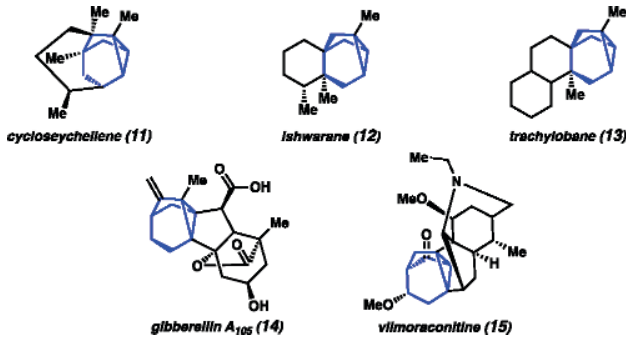


Figure 2. Natural products bearing a tricyclo[3.2.1.0]octane core.

1957[17] and substantiated by Coates and Bertram in 1971[18] for tetracyclic diterpenes such as kaurene and atisane.[19]

In the present work, we report computational and experimental studies on the thermal cyclization of aryl propargyl ethers **16** leading to tricyclo[3.2.1.0]octane adducts **17** and benzopyrans **18** (Figure 3). We use DFT calculations

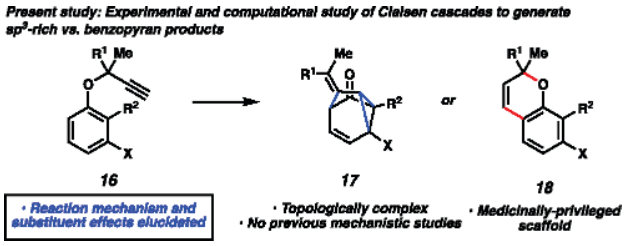


Figure 3. Present study of the reaction mechanism for intramolecular cyclization of **16** and substituent effects on product selectivity.

to elucidate the origins of selectivity for generating tetracycles related to adduct **17** versus benzopyran **18**. A better understanding of the fundamental reactivity of aryl propargyl ethers, the reaction mechanism of their Claisen cascades, and substituent effects on product distribution is presented.[20]

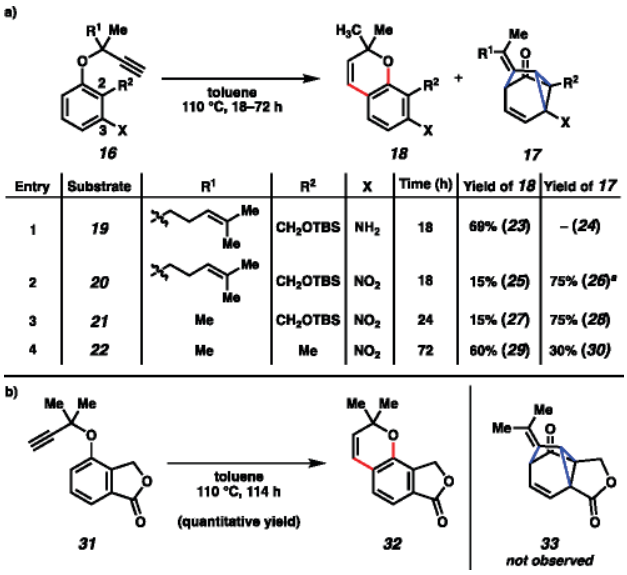
COMPUTATIONAL METHODS

Computations were performed using Gaussian 16.[21] Geometry optimizations were carried out using the B97X-D functional[22] and the 6-311+G(d,p) basis set. Solvation effects of toluene (PhMe) were also included using the solvation model based on density (SMD)[23] with a standard state of 1 M. Energy minima and transition states were verified through vibrational analysis. Frequency calculations were performed at the same theorical level as for geometry optimizations to verify the stationary points as either minima or first-order saddle points on the potential energy surface, as well as to obtain thermal Gibbs free energy corrections at 298 K. Truhlar s quasiharmonic correction was applied by setting all positive frequencies below 100 cm ^{1} to 100 cm ^{1}.[24] Optimized structures were illustrated using CYLview.[25]

RESULTS AND DISCUSSION

Experimental Comparison of the Claisen Cascades of Substituted Aryl Propargyl Ethers. In 2018, Hanessian and co-workers completed the first total syntheses of yaequinolones J1 and J2 using a key tandem aromatic Claisen rearrangement/electrocyclization strategy employing an aryl propargyl ether to construct the benzopyran core unit of both natural products.[9,26 28] In their efforts, substrate **19** was heated to re ux in toluene to successfully provide the benzopyran **23** bearing a homoprenyl chain in a 69 yield (Figure 4a, entry

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964



Entry	Substrate	R¹	R²	X	Time (h)	Yield of 18	Yield of 17
1	19		CH_2OTBS	NH_2	18	69% (23)	– (24)
2	20		CH_2OTBS	NO_2	18	15% (25)	75% (26)[a]
3	21	Me	CH_2OTBS	NO_2	24	15% (27)	75% (28)
4	22	Me	Me	NO_2	72	60% (29)	30% (30)

Figure 4. Experimental results for the Claisen cascades of (a) substituted aryl propargyl ethers **19** **22** and (b) lactone-fused aryl propargyl ether **31**. [a]Isolated as a 1:1 mixture of *E*/*Z* isomers.

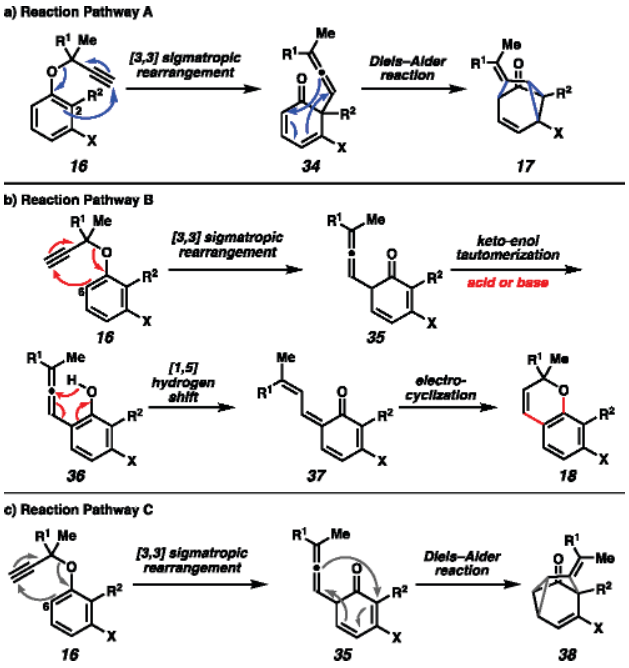


Figure 5. Proposed mechanistic pathways for conversion of aryl propargyl ether **16** to tetracycle **17**, benzopyran **18**, and alternate tetracycle **38**.

1). Following the total syntheses and absolute stereochemical assignment, yaequinolones J1 and J2 were found to exhibit activity against proliferating melanoma A375 and colorectal HTC116 cell lines.[9]

Although not disclosed in the 2018 publication,[9] under identical reaction conditions, nitro derivative **20** resulted in an unexpectedly low 15 yield of benzopyran **25** (Figure 4a, entry 2). Instead, tetracycle **26** was obtained as the major product in 75 yield, reminiscent of the reactivity previously observed by Zsindely and Schmid.[11] We were intrigued by the surprising result obtained with the nitro analog **20** compared to amino analog **19**, particularly because, in both cases, the reaction takes place in re uxing toluene compared to previously reported examples requiring drastically higher temperatures.[8,10,15] Reaction with substrate **21**, bearing a methyl group in place of the homoprenyl group, provided tetracycle **28** as the major product in 75 yield (Figure 4a, entry 3). The replacement of the alkylsiloxy group at C2 with a methyl group (substrate **22**) afforded benzopyran **29** in 60 yield and the crystalline tetracycle **30** in a 30 yield (Figure 4a, entry 4). The structure of this tetracyclic product was confirmed by single crystal X-ray analysis (see Supporting Information). In contrast, lactone derivative **31** provides exclusively benzopyran **32** after re uxing in toluene for 114 h (Figure 4b). With these experimental results in hand, we sought to computationally investigate the reaction mechanism for these transformations as well as substituent effects on reactivity and product distribution.

We propose three mechanistic pathways for formation of three potential products through the thermal cyclization of aryl propargyl ether **16** to form benzopyran product **18** and regioisomeric tetracycles **17** and **38**, all involving an initial Claisen rearrangement (Figure 5). In reaction pathway A, Claisen rearrangement at C2 of aryl propargyl ether **16** results in allene intermediate **34**, which subsequently participates in an intramolecular Diels Alder reaction to yield tetracycle **17** (Figure 5a). Notably, the ketone in allene **34** cannot tautomerize to an enol. In reaction pathway B, which leads to benzopyran product **18**, Claisen rearrangement at the less sterically hindered *meta*-position of aryl propargyl ether **16** (i.e., C6) provides alternate allene intermediate **35** (Figure 5b). Tautomerization of the ketone in allene **35** results in enol **36**, which then undergoes a 1,5-hydrogen shift to provide diene **37**. A final electrocyclization event provides benzopyran product **18**. Lastly, in reaction pathway C, Claisen rearrangement at C6 generates intermediate **35** which is followed by an intramolecular Diels Alder cycloaddition to provide adduct **38** (Figure 5c). Since isomeric product **38** has not been observed experimentally, we sought to understand why conversion of allene **35** to adduct **38** is disfavored over conversion to benzopyran **18**. Additionally, we wanted to understand if regioselectivity in the initial Claisen rearrangement in uences product distribution (i.e., ratio of benzopyran product **18** to tetracycle **17**) and, if so, to explain the origin of the selectivity.

Computational Study of the Claisen Cascades of Amino Substituted and Nitro Substituted Aryl Prop argyl Ethers. We initiated our computational studies by investigating the reaction mechanism for conversion of amino-substituted aryl propargyl ether **39** to benzopyran **46** and tetracyclic products **42** and **43** (Figure 6). A free energy profile for reaction pathways A and B leading to tetracyclic product **43** and benzopyran **46**, respectively, was generated. Reaction pathway C, involving generation of alternate tetracycle **42**, was also considered. The TBS protecting group in R^2 of substrate **19** was modeled with a TMS group, and the homoprenyl chain in R^1 was truncated to a methyl group. Claisen rearrangement at C2 of substrate **39** has a Gibbs free energy barrier (G) of 29.1 kcal mol ^{1} (**TS 2**) and is exergonic by 4.6 kcal mol ^{1}. The corresponding transition state, **TS 2**, is shown in Figure 6b. Subsequent intramolecular Diels Alder reaction of allene product **40** occurs via **TS 4** and with a kinetic barrier of 27.1 kcal mol ^{1} (Figure 6b). The energetics of reaction pathway B were evaluated next for substrate **39**. In this second pathway,

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964

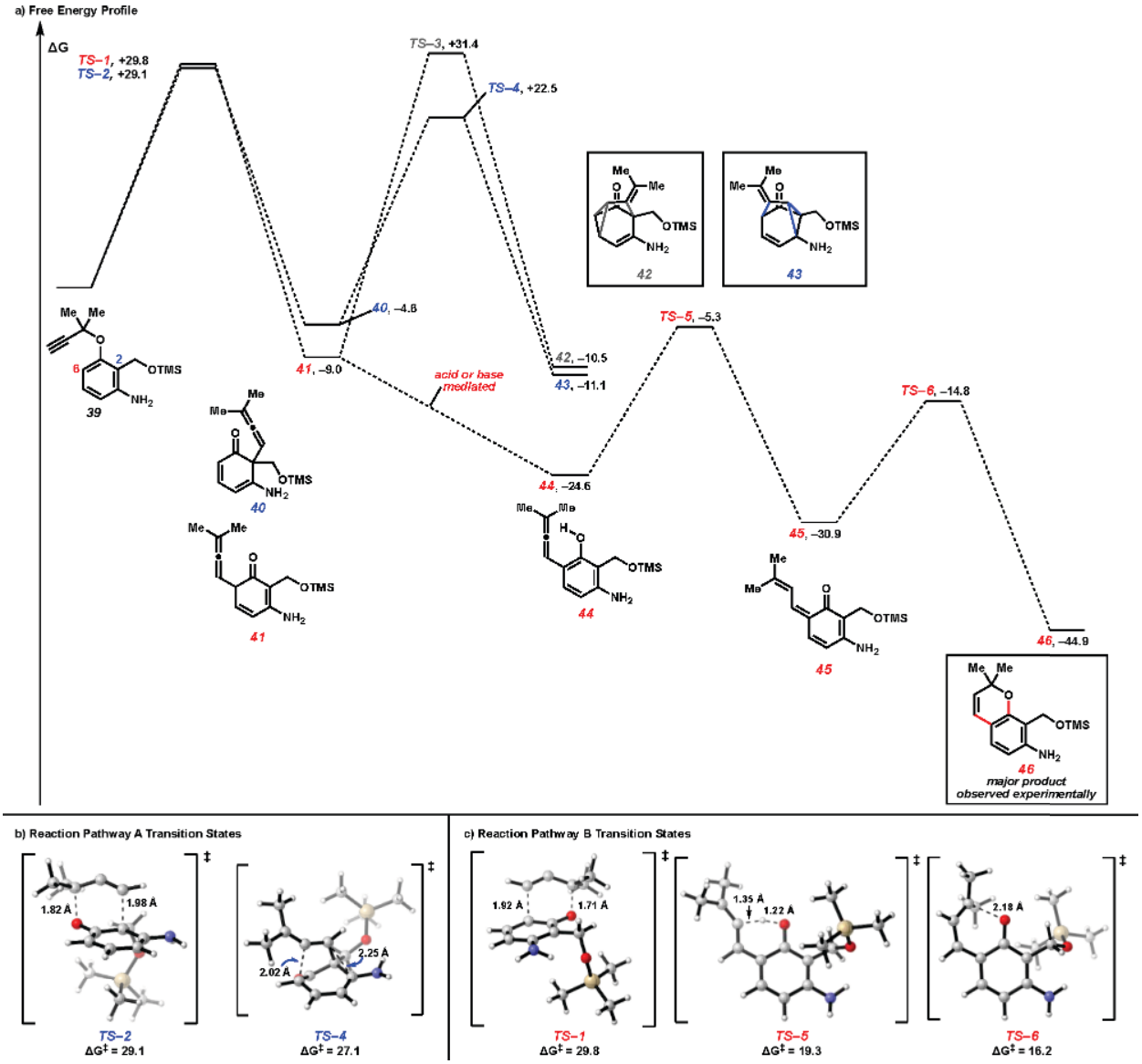


Figure 6. (a) Calculated free energies for the cascade reaction of **39** leading to products **42**, **43**, and **46** via reaction pathways A, B, and C. (b) Transition states for reaction pathway A. (c) Transition states for reaction pathway B. Energies are in units of kcal mol $^{-1}$.

G for the Claisen rearrangement at C6 of substrate **39** is 29.8 kcal mol $^{-1}$ (**TS 1**, Figure 6c). Acid or base mediated tautomerization of intermediate **41** to enol **44** occurs with a notable thermodynamic driving force (G = 15.6 kcal mol $^{-1}$).[29] Following tautomerization of ketone **41**, enol **44** undergoes a 1,5-hydrogen shift with G = 19.3 kcal mol $^{-1}$(**TS 5**). The resulting product, diene **45**, participates in a final electrocyclization with an energy barrier of 16.1 kcal mol $^{-1}$ to yield benzopyran **46**. Thus, our computations demonstrate that reaction pathways A and B for conversion of substrate **39** to products **43** and **46** respectively, both involve a rate-determining Claisen rearrangement as the first mechanistic step.

Reaction pathways A and B for cyclization of substrate **39** must be compared to understand why benzopyran **23** (Figure 4a, entry 1) is isolated as the major product in a 69 yield. Based on our calculations, the transition state for reaction at C6 (**TS 1**) is less stable than the transition state for Claisen rearrangement at C2 (**TS 2**) by 0.7 kcal mol $^{-1}$ (Figure 6a). However, the Claisen rearrangement at C6 mechanistically leads to benzopyran **23**, which is the experimentally observed product. Therefore, product distribution is not kinetically controlled. Instead, at elevated temperatures, reaction at C6 of aryl propargyl ether **39** becomes a reversible process. This reversibility allows for preferential generation of the more stable cyclohexadienone **41**, which funnels to benzopyran product **46** (Figure 6a). The greater stability of cyclohexadienone **41** relative to cyclohexadienone **40** (G = 4.4 kcal mol $^{-1}$) can be attributed to (1) the minimization of unfavorable steric interactions between the C2 and C3 substituents and (2) the presence of a more highly substituted double bond between C2 and C3 in cyclohexadienone **41**.

Intriguingly, our analysis of the reaction with nitro-substituted allyl propargyl ether **47** shows that preferential formation of tetracycle **51** is kinetically controlled. A free energy profile for cyclization of nitro-substituted substrate **47** via reaction pathways A and B was generated and is shown in Figure 7. In reaction pathway A, the Claisen rearrangement at

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964

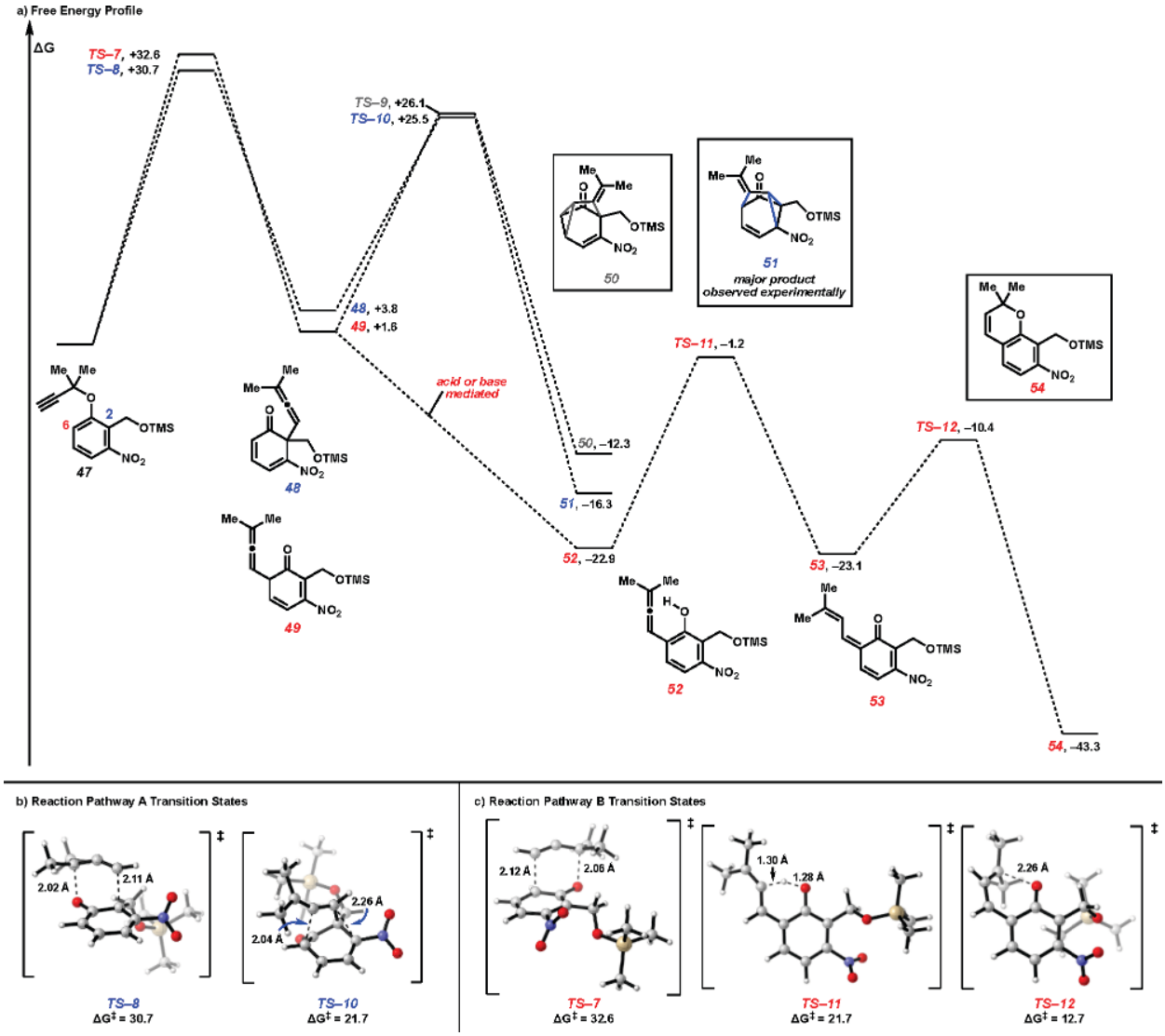


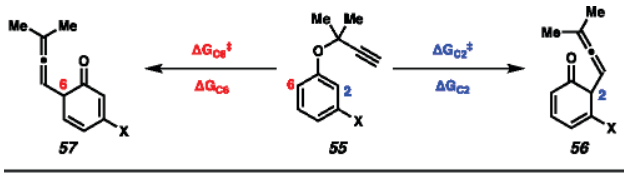
Figure 7. (a) Calculated free energies for the cascade reaction of **47** leading to products **50**, **51**, and **54** via reaction pathways A, B, and C. (b) Transition states for reaction pathway A. (c) Transition states for reaction pathway B. Energies are in units of kcal mol ^{1}.

C2 of substrate **47** occurs with G = 30.7 kcal mol ^{1}. Following the reaction at C2, allene intermediate **48** participates in an intramolecular Diels Alder reaction via **TS 10** with G of 21.7 kcal mol ^{1} (Figure 7b). For reaction pathway B, the Claisen rearrangement at C6 of substrate **47** has an energy barrier of 32.6 kcal mol ^{1} and is endergonic by 1.6 kcal mol ^{1}. The corresponding transition state for reaction at C6 (**TS 7**, Figure 7b) is kinetically disfavored over **TS 8** (Figure 7c) for the Claisen rearrangement at C2. After reaction at C6, allene intermediate **49** undergoes tautomerization to enol **52** with a strong thermodynamic driving force (G = 24.5 kcal mol ^{1}). A 1,5-hydrogen shift from enol **52** provides diene **53** (G = 21.7 kcal mol ^{1}), which then undergoes facile electrocyclization (G = 12.7 kcal mol ^{1}). Notably, the intramolecular Diels Alder reaction from allene **49** in reaction pathway C has a high energy barrier (**TS 9**, G = 24.5 kcal mol ^{1}) and is kinetically unfeasible.

A comparison of reaction pathways A and B for nitro-containing substrate **47** reveals that the Claisen rearrangement is more regioselective for substrate **47** (G = 1.9 kcal mol ^{1}) than for aniline **39** (G = 0.7 kcal mol ^{1}). As shown in Figure 4b, experiments demonstrate that thermal cyclization of the corresponding substrates **21** leads to tetracycle **28** in a 75 yield and benzopyran **27** in only a 15 yield. Thus, our results demonstrate that the introduction of a nitro group at C3 changes product selectivity, favoring the Claisen rearrangement toward C2. Notably, our computed G value of 1.9 kcal mol ^{1} for reaction at C2 of substrate **47** versus reaction at C6 suggests that tetracycle **28** (Figure 4a) should be isolated in quantitative yield. We attribute the discrepancy between the predicted yield of tetracycle **28** and experimental results (75 yield, Figure 4a) to a thermodynamic preference for reaction at C6 of substrate **21** over reaction at C2.

We presume that the Claisen rearrangement with nitro-containing substrate **47** is more regioselective than reaction with aniline **39** due to the electronic effects of the nitro group. To provide support for this presumption, substrates **58** and **59** were used as model systems to study the effects of the nitro group on reactivity and regioselectivity (Figure 8). Therefore, the corresponding G and G values for the Claisen rearrangement at C2 and C6 were calculated. Aryl propargyl ether **58**, which bears minimal substituents, participates in the

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964



Substrate	X	$\Delta G_{C6}^{\ddagger}$	ΔG_{C6}	$\Delta G_{C2}^{\ddagger}$	ΔG_{C2}
58[a]	H	+33.1	+0.6	–	–
59	NO_2	+33.3	+4.0	+31.7	+1.3

Figure 8. Reaction energetics for the Claisen rearrangement of model systems. Energies are in units of kcal mol ^{1}. [a]In the case where X = H, reactions at C2 and C6 generate the same product.

[3,3]-sigmatropic rearrangement with a kinetic barrier of 33.1 kcal mol ^{1}. Introduction of a nitro group at C3 of the aryl ring (i.e., substrate **59**) lowers G to 31.7 kcal mol ^{1} and directs the reaction to occur at C2 preferentially (G = 1.6 kcal mol ^{1}). Regioselectivity can be attributed to the electronic effects of the nitro group. In the corresponding transition state for the Claisen rearrangement at C2, the nitro group stabilizes the partial negative charge at C2 via inductive effects. As shown in Figure 5a, an amino group at C3 does not provide the same degree of stabilization in the corresponding transition state for the Claisen rearrangement at C2. Thus, switching the amino group at C3 as in substrate **39** to a nitro group as in substrate **47** increases regioselectivity in the initial Claisen rearrangement and favors formation of allene **40**, which mechanistically leads to tetracycle **43** (Figure 6a).

Despite containing a nitro group at C3, methylated aryl propargyl ether **22** generates benzopyran **29** with low selectivity (Figure 4a). The free energy profile in Figure 9a demonstrates that, in reaction pathways A and B, the [3,3]-sigmatropic rearrangements at C2 and C6 of substrate **22** are competing (G = 0.1 kcal mol ^{1}). In reaction pathway A, **TS 13** has a calculated energy of 31.9 kcal mol (Figure 9b). The resulting allene **60** participates in a subsequent intramolecular Diels Alder reaction via **TS 16** (G = 24.7 kcal mol ^{1}). In reaction pathway B, Claisen rearrangement at C6 of substrate **22** occurs via **TS 14** (Figure 9c) and results in allene intermediate **61**, which tautomerizes to enol **63** (G = 24.5 kcal mol ^{1}). The thermodynamic driving for keto enol tautomerization is higher for substrate **22** than for substrates **39** and **47** (Figures 6a and 5a, respectively). The subsequent mechanistic steps are thermodynamically downhill. A 1,5-hydrogen shift event converts enol **63** to *trans* diene **64** via **TS 17** with an energy barrier of 22.8 kcal mol ^{1}. Electrocyclization provides final product **29**. Experimentally, the thermal cyclization of methylated substrate **22** results in a 60 yield of benzopyran analogue **29** and 30 yield of tetracycle **30** (Figure 4a). Our calculations show that low product selectivity is observed due to the low regioselectivity in the Claisen rearrangement and thermodynamic reversibility in the reaction at C6. The Claisen rearrangement has low regioselectivity

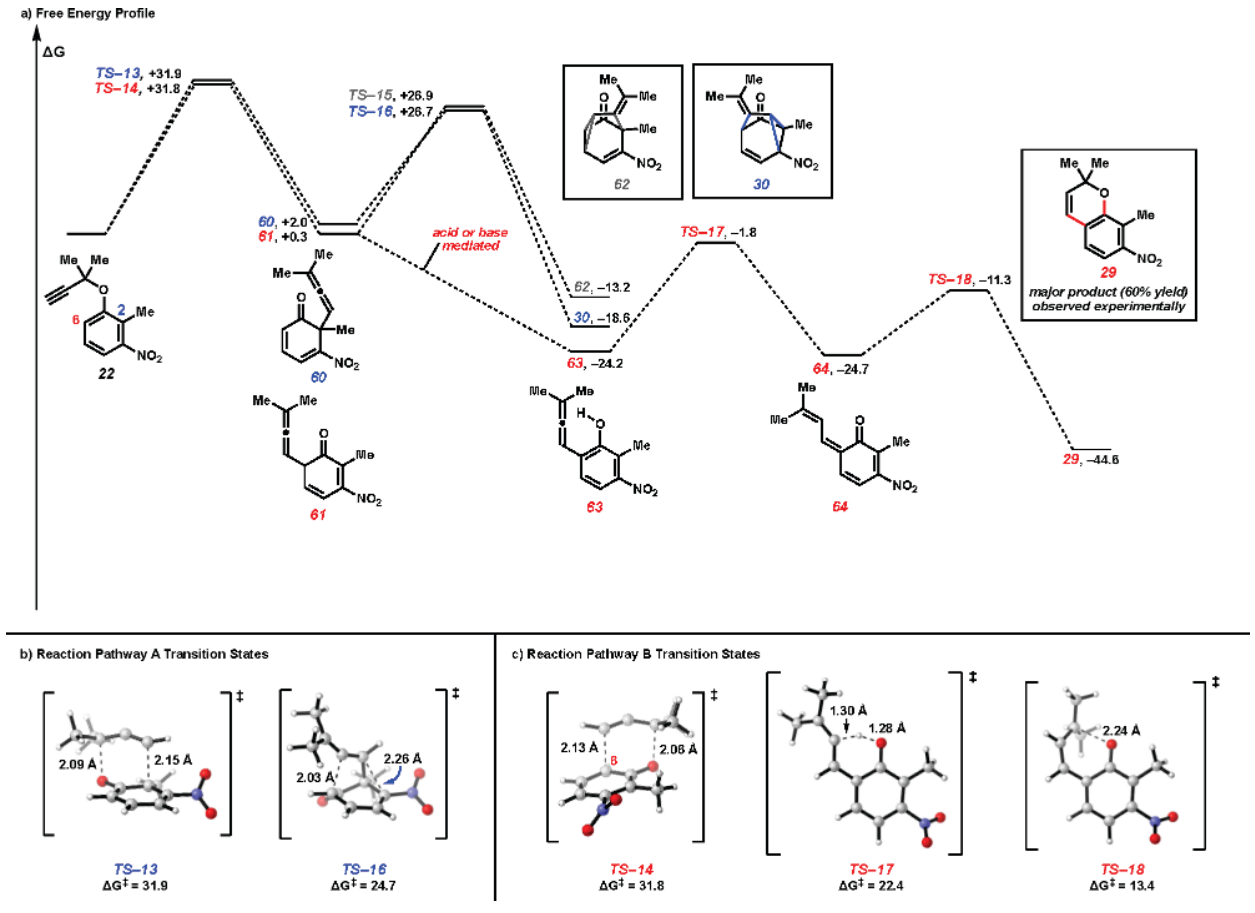


Figure 9. (a) Calculated free energies for the cascade reaction of **22** leading to products **62**, **30**, and **29** via reaction pathways A, B, and C. (b) Transition states for reaction pathway A. (c) Transition states for reaction pathway B. Energies are in units of kcal mol ^{1}.

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964

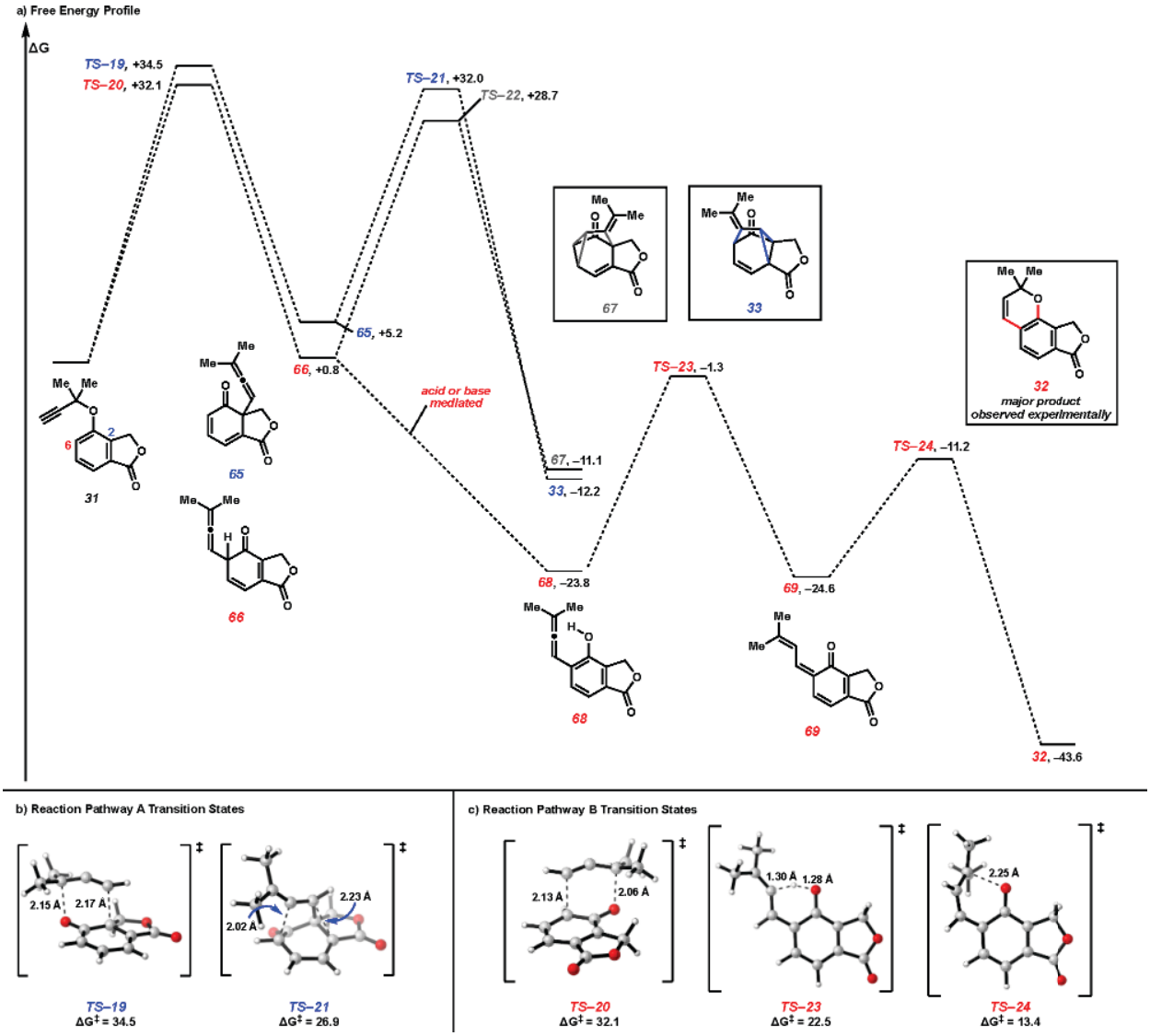


Figure 10. (a) Calculated free energies for the cascade reaction of **31** leading to products **67**, **33**, and **32** via reaction pathways A, B, and C. (b) Transition states for reaction pathway A. (c) Transition states for reaction pathway B. Energies are in units of kcal mol ^{1}.

because the alkylsiloxy group is no longer present at C2 (i.e., as in substrates **39** and **47**) and cannot stabilize **TS 13** via inductive effects. Additionally, Claisen rearrangement at C6 in reaction pathway B is reversible, meaning that formation of allene intermediate **61**, which leads to benzopyran **29**, does not have a strong thermodynamic driving force. Thus, both kinetics and thermodynamics contribute to the lower selectivity for generation of benzopyran **29** over tetracycle **30** from substrate **22**.

Computational Study of the Claisen Cascades of Lactone Fused Aryl Propargyl Ethers. Theoretical analysis of the reaction cascade involving lactone-fused substrate **31** shows a strong kinetic preference for the Claisen rearrangement at C6. Based on our calculations for reaction pathways A and B, the Claisen rearrangement is highly regioselective and occurs preferentially at C6 via **TS 20** with a kinetic barrier of 32.1 kcal mol ^{1} (Figure 10a). Among all substrates analyzed in this study, substrate **31** has the highest selectivity for reaction at C2 versus C6 (G = 2.4 kcal mol ^{1}). For substrates **39**, **47**, and **22**, G ranges from 0.1 to 1.9 kcal mol ^{1}. The high regioselectivity predicted in this mechanistic step for substrate **31** is attributed to (1) the steric effects of its fused lactone, which makes reaction at C2 highly disfavored, and (2) the lack of a strongly inductively withdrawing group at C3. This is supported by the high energy barrier calculated for the Claisen rearrangement at C2 of substrate **31** via **TS 19** (Figure 10b, G = 34.5 kcal mol ^{1}), which is highest among all substrates we studied in this report. Additionally, formation of allene intermediate **66** in reaction pathway B is much less endergonic than the formation of allene **65** in reaction pathway A. The lower endergonicity predicted for the Claisen rearrangement at C6 is associated with the minimization of unfavorable steric interactions between the C2 and C3 substituents in allene **66** when compared to allene **65**. In reaction pathway B, or the favored reaction pathway, allene **66** is readily converted to enol **68** with high exergonicity (G = 24.6 kcal mol ^{1}). 1,5-Hydrogen shift of enol **68** via **TS 23** and electrocyclization of diene **69** via **TS 24** leads to benzopyran **32** (Figure 9c). Both mechanistic steps have lower energy barriers (G = 13.4 22.5 kcal mol ^{1}) than the initial Claisen rearrangement at C6

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964

(G = 32.1 kcal mol ^{1}). Overall, our computations demonstrate that benzopyran **32** is generated with high selectivity due to the strong kinetic and thermodynamic preference for the Claisen rearrangement at C6 of lactone **31**.

Computational Study of the Original Claisen Cascade Reaction of Aryl Propargyl Ethers. In the light of the above computational and experimental results, we deemed it useful to study the original Zsindely and Schmid thermal Claisen rearrangements of 2,6-dimethyl-1-phenyl propargyl ether **4**, as well as the corresponding hydroxymethyl analogue **9** (Figure 1b). In both cases, the bridged cyclopropane products **5** and **10** were favored over the corresponding benzopyrans respectively (see Supporting Information for details).

CONCLUSIONS

We report experimental and computational studies on the thermal cyclization of aryl propargyl ethers leading to bridged tetracyclic cyclohexenones harboring a fused cyclopropane ring, and to substituted benzopyrans. The mechanism for these reactions involves a rate-determining Claisen rearrangement as the first mechanistic step. Rearrangement at C2 ultimately leads to a fused cyclopropane product within a tricyclo[3.2.1.0]octane core, whereas the rearrangement at C6 leads to a benzopyran product. The [3,3]-sigmatropic rearrangement at C6 of the substrate is exergonic if an intramolecular hydrogen bond is introduced in the product. Exergonicity of this first mechanistic step can result in preferential formation of benzopyran product. Notably, the Claisen rearrangement at C2 is thermodynamically disfavored over reaction at C6. However, the transition state for the Claisen rearrangement at C2 can also be electronically stabilized via introduction of an electron withdrawing nitro group at C3. Selective formation of fused cyclopropane rings systems from aryl propargyl ethers can be achieved through a combination of kinetic and thermodynamic control so that the Claisen rearrangement at C2 of the substrate is favored. The present study represents the first computational analysis of the mechanism of the cyclization of aryl propargyl ethers leading to tricyclo[3.2.1.0]octanes, which had been experimentally reported for the first time over 50 years ago.[11] In this context, our investigation is also one of the few theoretical studies on the Claisen rearrangement/electrocyclization cascade leading to benzopyrans and the effect of substitution on reactivity. We anticipate that our study will enable further synthetic method development and expansion of this historically important reaction in accessing architecturally complex natural products.[27]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02296.

Detailed experimental procedures, compound characterization data, and computational analysis (PDF)

Accession Codes

CCDC 1902484 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, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Stephen Hanessian *Department of Chemistry, Universit de Montr al, Montr al, Qu bec, Canada H3C3J7*; orcid.org/0000-0003-3582-6972; Email: stephen.hanessian@umontreal.ca

K N Houk *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; orcid.org/0000-0002-8387-5261; Email: houk@chem.ucla.edu

Authors

Melissa Ramirez *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States*; orcid.org/0000-0002-4038-2029

Vito Vece *Department of Chemistry, Universit de Montr al, Montr al, Qu bec, Canada H3C3J7*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c02296

Author Contributions

M.R. completed all computational work, and V.V. performed experimental work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the National Science Foundation (CHE-1764328 to K.N.H.) and the University of California, Los Angeles for financial support. This study used computational and storage services associated with the Hoffman2 Shared Cluster provided by UCLA Institute for Digital Research and Education s Research Technology Group. S.H. and V.V. acknowledge financial support from the National Science and Engineering Council of Canada.

REFERENCES

(1) Claisen, L. Über Umlagerung von Phenol allyläthern in C Allyl phenole. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157 3166.

(2) See for example: (a) Martin Castro, A. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939 3002. (b) Ziegler, F. E. The Thermal, Aliphatic Claisen Rearrangement. *Chem. Rev.* **1988**, *88*, 1423 1452. (c) Ito, H.; Taguchi, T. *Aromatic Claisen Rearrangement in The Claisen Rearrangement Methods and Applications*; Wiley-VCH: Weinheim, 2007.

(3) (a) Knochel, P., Molander, G. A., Eds. *Claisen Rearrangements: Comprehensive Organic Synthesis*, 2nd ed.; Elsevier: Oxford, 2014. (b) Bennett, G. B. The Claisen Rearrangement in Organic Synthesis; 1967 to January 1977. *Synthesis* **1977**, *1977*, 589 606.

(4) For a recent example, see: Fulton, T. J.; Cusumano, A. Q.; Alexy, E. J.; Du, Y. E.; Zhang, H.; Houk, K. N.; Stoltz, B. M. Global Diastereoconvergence in the Ireland-Claisen Rearrangement of Isomeric Enolates: Synthesis of Tetrasubstituted α-Amino Acids. *J. Am. Chem. Soc.* **2020**, *142*, 21938 21947.

(5) Claisen and Eisleb reported the simplest rendition of the *ortho*-Claisen rearrangement, which involves the thermal transposition of an allyl phenyl ether into 3-allyl phenol; see: (a) Claisen, L.; Eisleb, O. Über Die Umlagerung von PhenolallyläthernIn Die Isomeren Allylphenole. *Justus Liebigs Ann. Chem.* **1913**, *401*, 21 119. (b) Claisen, L.; Tietze, E. Über den Mechanismus der Umlagerung der Phenol-allyläther. *Ber. Dtsch. Chem. Ges. B* **1925**, *58*, 275 281.

(6) For seminal studies on the aromatic Claisen rearrangement and substituent effects, see: (a) White, W. N.; Slater, C. D. The ortho-Claisen Rearrangement. V. The Products of Rearrangement of Allyl

m-X-Phenyl Ethers. *J. Org. Chem.* **1961**, *26*, 3631 3638. (b) White, W. N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W. The ortho-Claisen Rearrangement. I. The Effect of Substituents on the Rearrangement of Allyl p-X-Phenyl Ethers. *J. Am. Chem. Soc.* **1958**, *80*, 3271 3277. (c) Goering, H.; Jacobson, R. R. A Kinetic Study of the ortho-Claisen Rearrangement. *J. Am. Chem. Soc.* **1958**, *80*, 3277 3285. (d) Marvell, E. N.; Stephenson, J. L.; Dupzyk, R. J.; Stephenson, J. L.; Anderson, R. Stereochemistry of the Claisen Rearrangement. *J. Org. Chem.* **1960**, *25*, 608 611. (e) White, W. N.; Fife, W. K. The ortho-Claisen Rearrangement. IV. The Rearrangement of X-Cinnamyl p-Tolyl Ethers. *J. Am. Chem. Soc.* **1961**, *83*, 3846 3853. (f) Burgstahler, A. W. The Steric Course of the Claisen Rearrangement. *J. Am. Chem. Soc.* **1960**, *82*, 4681 4685. (g) Huestis, L. D.; Andrews, L. J. The Effect of Geometry in the Allyl Group on the Rate of the Claisen Rearrangement. *J. Am. Chem. Soc.* **1961**, *83*, 1963 1968. (h) White, W. N.; Norcross, B. E. The Effect of Geometry in the Allyl Group on the Rate of the Claisen Rearrangement. *J. Am. Chem. Soc.* **1961**, *83*, 1968 1974.

(7) For a study of substituent effects on the aromatic Claisen rearrangement of *meta*-substituted allyl phenyl ethers, see: Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. Regioselectivity in Aromatic Claisen Rearrangements. *J. Org. Chem.* **2003**, *68*, 5493 5499.

(8) (a) Iwai, I.; Ide, J. Studies an Acetylenic Compounds. XXIII. A New Ring Closure of 2-Propynyl Ethers. *Chem. Pharm. Bull.* **1962**, *10*, 926 933. (b) Iwai, I.; Ide, J. Studies on Acetylenic Compounds. XXXII. Ring Closure of Propargyl Ethers. *Chem. Pharm. Bull.* **1963**, *11*, 1042 1049.

(9) Vece, V.; Jakkepally, S.; Hanessian, S. Total Synthesis and Absolute Stereochemical Assignment of the Insecticidal Metabolites Yaequinolones J1 and J2. *Org. Lett.* **2018**, *20*, 4277 4280.

(10) For natural product syntheses utilizing the Claisen cascade of aryl propargyl ethers, see: (a) Ishii, H.; Ishikawa, T.; Takeda, S.; Suzuki, M.; Harayaya, T. Total Synthesis of Chelerythrine, a Benzo[c]phenanthridine Alkaloid. *Chem. Pharm. Bull.* **1992**, *40*, 2002 2006. (b) Hesse, R.; Gruner, K. K.; Kataeva, O.; Schmid, A. W.; Knölker, H.-J. Efficient Construction of Pyrano[3,2 a]carbazoles: Application to a Biomimetic Total Synthesis of Cyclized Monoterpenoid Pyrano[3,2 a]carbazole Alkaloids. *Chem. - Eur. J.* **2013**, *19*, 14098 14111. (c) Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. Cesium Fluoride-Mediated Claisen Rearrangement of Aryl Propargyl Ether. Exclusive Formation of 2-Methylarylfuran and Its Availability as a Masked Salicylaldehyde. *Chem. Pharm. Bull.* **1992**, *40*, 1148 1153. (d) Yang, Z.-Y.; Xia, Y.; Xia, P.; Brossi, A.; Lee, K.-H. A Concise Regiospecific Synthesis of 8,8-Dimethyl-2H, 8H-Pyrano[6,5-h]quinolin-2-one and Related Compounds. *Tetrahedron Lett.* **1999**, *40*, 4505 4506.

(11) Zsindely, J.; Schmid, H. Sigmatropische Umlagerungen von Aryl propargyläthern; Synthese von 1,5 Dimethyl 6 methylen tricyclo[3,2,1,02,7] oct 3 en 8 on Derivaten. *Helv. Chim. Acta* **1968**, *51*, 1510 1514.

(12) For experimental studies on substituent effects on the reactivity of aryl propargyl ethers in thermal cyclizations, see: Anderson, W. K.; LaVoie, E. J. Thermal Cyclization of Substituted Aryl Propargyl Ethers. Scope of Regioselectivity of the Reaction in the Synthesis of Substituted 3-Chromenes. *J. Org. Chem.* **1973**, *38*, 3832 3835. (b) Anderson, W. K.; LaVoie, E. J.; Whitkop, P. G. Steric and Electronic Factors Which Effect the Thermal Cyclization of Meta-Substituted Aryl Propargyl Ethers. Synthesis of 5- and 7-Substituted 3-Chromenes. *J. Org. Chem.* **1974**, *39*, 881 884. (c) Harfenist, M.; Thom, E. The Influence of Structure on the Rate of Thermal Rearrangement of Aryl Propargyl Ethers to the Chromenes. The gem-Dimethyl Effect. *J. Org. Chem.* **1972**, *37*, 841 848. (d) Roa, U.; Balasubramanian, K. K. Claisen Rearrangement of Aryl Propargyl Ethers in Poly(ethylene glycol)-A Remarkable Substituent and Solvent Effect. *Tetrahedron Lett.* **1983**, *24*, 5023 5024.

(13) Extensive efforts have been made to understand regioselectivity in the Claisen rearrangement of phenyl allyl ethers using both experiments and computations. For example, White and Slater (ref 6a) previously proposed that the electronic nature of the *meta*-substituent in phenyl allyl ethers overrides steric effects on regioselectivity. For substrates containing an electron-withdrawing substituent such as a cyano or benzoyl group, reaction occurred regioselectively at the 2 position, or the sterically hindered *ortho* position. In contrast, for substrates bearing an electron-donating group, reaction occurred selectively at the less sterically hindered 2 position of the substrate. In 2003, Marsaioli and co-workers (ref 7) also studied substituent effects on regioselectivity in the aromatic Claisen rearrangements of *meta*-substituted phenyl allyl ethers using B3LYP/6-31G(d, p).

(14) Mechanistically, benzofurans **2** are formed through Claisen rearrangement to form an allene intermediate.

(15) (a) Srinivasadesikan, V.; Dai, J.-K.; Lee, S.-L. Quantum Mechanistic Insights on Aryl Propargyl Ether Claisen Rearrangement. *Org. Biomol. Chem.* **2014**, *12*, 4163 4171. (b) Menkir, M. G.; Srinivasadesikan, V.; Lee, S.-L. The Role of Cesium Fluoride in Aryl Propargyl Ether Claisen Rearrangement and its Mechanistic Elucidation: A Theoretical Study. *Struct. Chem.* **2016**, *27*, 1383 1393.

(16) The thermal cyclization of aryl propargyl ether has been demonstrated to provide cyclohexadienone products where the proposed mechanism involves tetracyclic intermediates similar to fused ring system **5**. For examples of the thermal cyclization of aryl propargyl ethers leading to cyclohexadienones, see: (a) Trahanovsky, W. S.; Mullen, P. W. Formation of 2-Indanone and Benzocyclobutene from the Pyrolysis of Phenyl Propargyl Ether. *J. Am. Chem. Soc.* **1972**, *94*, 5911 5913. (b) Riemann, J. M.; Trahanovsky, W. S. Formation of Methyl-Substituted 2-Indanones and 1,2-Dihydrobenzo-Cyclobutenes by the Pyrolysis of o-, m-, and p-Tolyl Propargyl Ethers. *Tetrahedron Lett.* **1977**, *18*, 1863 1866. (c) Barmettler, P.; Hansen, H.-J. Acid-Catalyzed [3,3]-Sigmatropic Rearrangements of N-Propargylanilines. *Helv. Chim. Acta* **1990**, *73*, 1515 1573. (d) Quinkert, G.; Scherer, S.; Reichert, D.; Nestler, H. P.; Wennemers, H.; Ebel, A.; Urbahns, K.; Wagner, K.; Michaelis, K. P.; Wiech, G.; Prescher, G.; Bronstert, B.; Freitag, B.-J.; Wicke, I.; Lisch, D.; Belik, P.; Crecelius, T.; Hörstermann, D.; Zimmermann, G.; Bats, J. W.; Dürner, G.; Rehm, D. Stereoselective Ring Opening of Electronically Excited Cyclohexa-2,4-dienones: Cause and Effect. *Helv. Chim. Acta* **1997**, *80*, 1683 1772.

(17) Wenkert, E. Structural and Biogenetic Relationships in the Diterpene Series. *Chem. Ind. London)* **1955**, *36*, 282 284.

(18) Coates, R.; Bertram, E. Biogenetic- Like Rearrangements of Tetracyclic Diterpenes. *J. Org. Chem.* **1971**, *36*, 3722 3729.

(19) Abad, A.; Agullo, C.; Cunat, A. C.; de Alfonso Marzal, I.; Navarro, I.; Gris, A. A Unified Synthetic Approach to Trachylobane-, Beyerane-, Atisane- and Kaurane- Type Diterpenes. *Tetrahedron* **2006**, *62*, 3266 3283.

(20) Portions of this manuscript are from the doctoral dissertation of Melissa Ramirez, see:Ramirez, M. (2021). *Investigations of Strained Cyclic Intermediates and Pericyclic Reactions for Complex Molecule Synthesis*. UCLA. ProQuest ID, Ramirez_ucla_0031D_19685. Merritt ID: ark:/13030/m53j9dnq. Retrieved from https://escholarship.org/uc/item/02s0s6k0.

(21) See the Supporting Information for full citation of Gaussian 16.

(22) Chai, J.-D.; Head-Gordon, M. Long-Range Corrected Hybrid Density Functionals with Damped Atom-Atom Dispersion Corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615 6620.

(23) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielec- tric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378 6396.

(24) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Use of Solution-Phase Vibrational Frequencies in Continuum Models for the Free Energy of Solvation. *J. Phys. Chem. B* **2011**, *115*, 14556 14562.

(25) Legault, C. Y. *CYLView, 1.0b*; Université de Sherbrooke: Quebec, Montreal, Canada, http://www.cylview.org (2009).

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964

(26) In 2005, Omura and co-workers reported the isolation of yaequinolones J1 and J2 and assigned their relative stereochemistries based on extensive NMR studies: Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. Yaequinolones J1 and J2, Novel Insecticidal Antibiotics from Penicillium sp. FKI-2140. *Org. Lett.* **2005**, *7*, 5701 5704.
(27) For a recent total synthesis, see: Schwan, S.; Kleoff, M.; Heretsch, P.; Christmann, M. Five Step Synthesis of Yaequinolones J1 and J2. *Org. Lett.* **2020**, *22*, 675 678.
(28) These metabolites belong to a restricted class of 3,4-dioxygenated 3,4-dihydroquinolones exhibiting insecticidal activity; see: Simonetti, S. O.; Larghi, E. L.; Kaufman, T. S. The 3,4-Dioxygenated 5-Hydroxy-4-aryl-quinolin-2(1H)-one Alkaloids. Results of 20 Years of Research, Uncovering a New Family of Natural Products. *Nat. Prod. Rep.* **2016**, *33*, 1425 1446.
(29) *G* for keto enol tautomerization was not calculated because the identity of the acid or base is unknown.

https://doi.org/10.1021/acs.joc.1c02296
J Org Chem 2021 86 17955 17964