Article

An unexpected Ireland–Claisen rearrangement cascade during the synthesis of the tricyclic core of Curcusone C: Mechanistic elucidation by trial-and-error and automatic artificial force-induced reaction (AFIR) computations

Chung Whan Lee, Buck L. H. Taylor, Galina P. Petrova,
Ashay Patel, Keiji Morokuma, K. N. Houk, and Brian M. Stoltz

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 25 Mar 2019

An unexpected Ireland–Claisen rearrangement cascade during the synthesis of the tricyclic core of Curcusone C: Mechanistic elucidation by trial-and-error and automatic artificial force-induced reaction (AFIR) computations

Chung Whan Lee,[†‖§] Buck L. H. Taylor,[‡▽§] Galina P. Petrova,[⊥] Ashay Patel,[‡#] Keiji Morokuma,[⊥¶a] K. N. Houk,[‡*] Brian M. Stoltz[†*]

[†]Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

[⊥]Fukui Institute for Fundamental Chemistry, Kyoto University, Kyoto 606-8103, Japan

[a] Deceased November 27, 2017

KEYWORDS natural products, unexpected rearrangement, curcusone, total synthesis, divinylcyclopropane rearrangement

ABSTRACT: In the course of a total synthesis effort directed toward the natural product curcusone C, the Stoltz group discovered an unexpected thermal rearrangement of a divinylcyclopropane to the product of a formal Cope/1,3-sigmatropic shift sequence. Since the involvement of a thermally forbidden 1,3-shift seemed unlikely, theoretical studies involving two approaches, the "trial-and-error" testing of various conceivable mechanisms (Houk group) and an "automatic" approach using the Maeda–Morokuma AFIR method (Morokuma group) were applied to explore the mechanism. Eventually, both approaches converged on a cascade mechanism shown to have some partial literature precedent: Cope rearrangement/1,5-sigmatropic silyl shift/Claisen rearrangement/retro-Claisen rearrangement/1,5-sigmatropic silyl shift, comprising a quintet of five sequential thermally-allowed pericyclic rearrangements.

1. Introduction

In the course of multistep total synthesis efforts directed toward a complex molecule, organic chemists sometimes serendipitously discover unexpected structures that arise from unknown rearrangement cascades. It is often difficult to determine the reaction mechanism. Besides the chemists' intrinsic curiosity about how the reaction occurs, it is important to investigate an unexpected reaction to understand its potential mechanism in order to expand the potential of the reaction. Computation has become an important tool to assist in mechanistic reasoning.[1] As density functional theory (DFT) methods have become more able to deal with the relatively large (for theory) molecules studied by synthetic chemists, it has become an able partner with experiment in exploring mechanism. This paper describes a synthetic approach to curcusone C, interrupted by an unexpected skeletal rearrangemented. Because the mechanism of this rearrangement was not clear, and the only likely possibility is forbidden by the Woodward–Hoffmann rules, computations were undertaken to uncover other plausible mechanisms.

The conventional approach to computational mechanism elucidation involves first selecting a method, nowadays one of the DFT methods, that will give accurate (± 1 or 2 kcal/mol) energetics for the atoms involved and the types of mechanisms likely to occur. Various mechanisms are then explored, guided by chemical intuition and prior results. Intermediates and transition states are optimized to obtain energetics for each proposed mechanism, and pathways with activation energies too high to be possible are eliminated from consideration. We refer to this procedure as the "trial-and-error" approach. Generally, one mechanism consistent with experimental rates is obtained in this way, but it is always possible that the actual mechanism has not been discovered.

Because of this lingering concern about overlooking the "global minimum mechanism," or to avoid the use of chemical intuition, chemists have developed new algorithms to predict mechanisms.[2,3] One of these, AFIR (artificial force-induced reaction), devised by Maeda and Morokuma, involves applying forces to stretch bonded atoms apart or force non-bonded atoms together, and then a series of calculations to map out low energy mechanisms from reactant to product.[2] This has led to a family of such methods and reasonable success in finding known mechanisms and sometimes discovering new mechanisms. Other methods such as Martinez's "nanoreactor" use high temperature molecular dynamics to determine reaction mechanisms, but this method has been applied only to small gas-phased processes.[3] MNY methods, such as Chandler's "throwing ropes over rough mountain passes – in the

dark,"[4] or Zimmerman's "Growing String Method"[5] are more or less automatic ways of finding transition states for conversion of one molecule to another but require intensive calculations to locate the lowest energy pathway. All of these methods are designed to find the best pathway across a potential surface to convert reactants into products, but are less appropriate for multi-step mechanisms that often occur in organic chemistry.

In the course of synthetic studies by the Stoltz group toward the natural product curcusone C, an unexpected reaction product was encountered from a synthetic intermediate. Challenged to use computations to determine the mechanism of the reaction, the Houk and Morokuma groups agreed to test the conventional "trial-and-error" and the automatic Maeda–Morokuma AFIR methods. The calculations were performed by the Houk and Morokuma groups, respectively. We wished to see which method worked best and the relative time needed to determine an unknown mechanism for a real organic problem. In the event, Morokuma's group using AFIR, and Houk's group, using the "trial-and-error" methods, converged on the same mechanism for which experimental analogy was then found in the chemical literature. Both took about one year of part-time human effort and significant computer time. This paper describes a general mechanism for the unusual reaction discovered and provides an assessment of the aptitudes of currently available methods to solve such problems.

2. Background

Native to Central America, *Jatropha curcas* is a species of flowering plant belonging to the Euphorbiaceae family that can be found in many parts of the world. *J. curcas* has been used as a source of soap and lamp oil for hundreds of years, and recently *J. curcas* has attracted attention due to its possible use in biodiesel production.[6]

J. curcas has intrigued natural product chemists as a source of versatile diterpenoids. Diterpenes curcusones A–D (**1**–**4**), which possess novel tricyclic skeletons, were isolated by Naengchomnong and co-workers in 1986.[7a] The structures of curcusones B (**2**) and C (**3**) were confirmed by X-ray diffraction analysis. Primary NMR data indicated that curcusones A (**1**) and B (**2**) were epimeric at C(2), as were curcusones C (**3**) and D (**4**). Recently, *J. curcas* has been further investigated and yielded more natural products. In 2011, Taglialatela-Scafati and co-workers reported curcusone E (**5**) and spirocurcasone (**11**) as other secondary metabolites isolated from the plant and again found curcusones A–E.[7b] Furthermore, curcusones F–J (**6**-**10**) and 4-*epi*-curcusone E were discovered in 2013 (Figure 1), although the originally proposed structures of curcusones I and J have been called into question.[7c,e] Among curcusones A–E and spirocurcasone, curcusone C has the greatest antiproliferative activity on L5178 cell lines (mouse lymphoma, IC_{50} in 0.08 μg mL^{-1}).[7b] Furthermore, curcusone C exhibited considerable potency toward HL-60 (human promyelocytic leukemia, IC_{50} in 1.36 μM),[7c] SMMC-7221 (human heptoma, IC_{50} in 2.17 μM),[7c] A-549 (adenocarcinomic human alveolar basal epithelial, IC_{50} in 3.88 μM),[7c] MCF-7 (human breast cancer, IC_{50} in 1.61 μM),[7c] SW480 (human colon adenocarcinoma, IC_{50} in 1.99 μM),[7c] and SK-OV3 (human ovarian cancer, IC_{50} in 0.160 μM)[7d] cell lines.

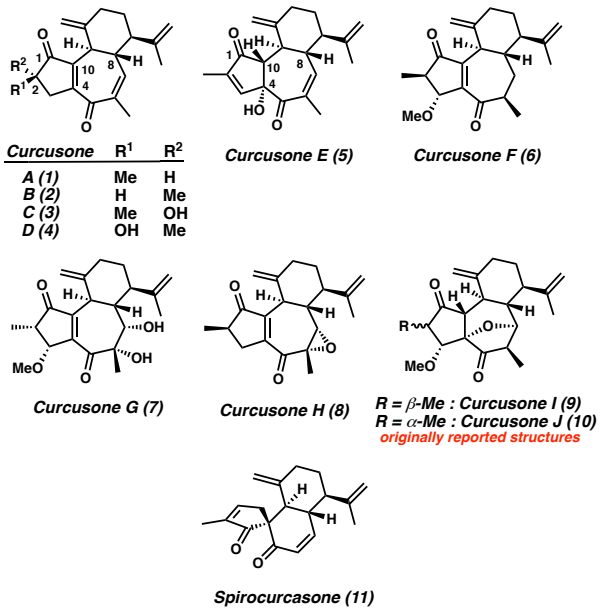


Figure 1. Curcusones A–J (**1–10**) and Spirocurcasone (**11**).

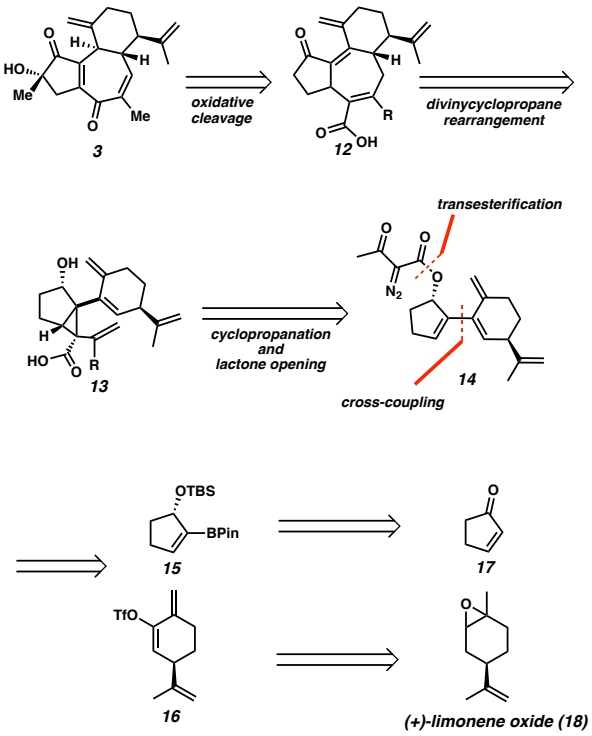
Curcusones (**1**–**10**) possess novel tricyclic skeletons featuring a 2,3,7,8-tetrahydroazulene-1,4-dione moiety with four stereogenic carbon centers. Since the initial isolation in 1986, a completed total synthesis has not been reported, although Dai recently completed elegant syntheses of the proposed structures of curcusones I and J (**9** and **10**), but unfortunately the data for the synthetic material did not match the isolation spectra, calling the original structural assignments into question.[7e] Additionally, one methodological study for the construction of the 7-membered ring of curcusones A–D was reported in 2001.[8] These interesting biological properties and structural features make the curcusones attractive targets, inspiring us to undertake the total synthesis of curcusone C (**3**).

3. Results and Discussion

3.1. Retrosynthetic analysis; Divinylcyclopropane rearrangement strategy to curcusone C.

Our retrosynthetic analysis of curcusone C **3** is outlined in Scheme 1. We envisioned that natural product **3** could be synthesized by oxidative cleavage, and olefin migration followed by alpha carbon functionalization of tricyclic core **12**. The tricyclic core **12** could be prepared by divinylcyclopropane rearrangement of cyclopropane **13** in a stereospecific fashion by an *endo*-boat transition state. Construction of cyclopropane **13** could be achieved via intramolecular cyclopropanation followed by lactone opening of diazo ester **14**. Cyclopropanation precursor **14** could be disconnected by transesterification followed by diazo transfer of allylic alcohol, which itself would be assembled by cross-coupling of vinyl boronic ester **15** and vinyl triflate **16**. Vinyl boronic ester **15** would be prepared from cyclopentenone **17** according to literature precedent,[9] and vinyl triflate **16** would be prepared from triflation of a known ketone[10] derived from (+)-limonene oxide (**18**).

Scheme 1. Retrosynthetic analysis

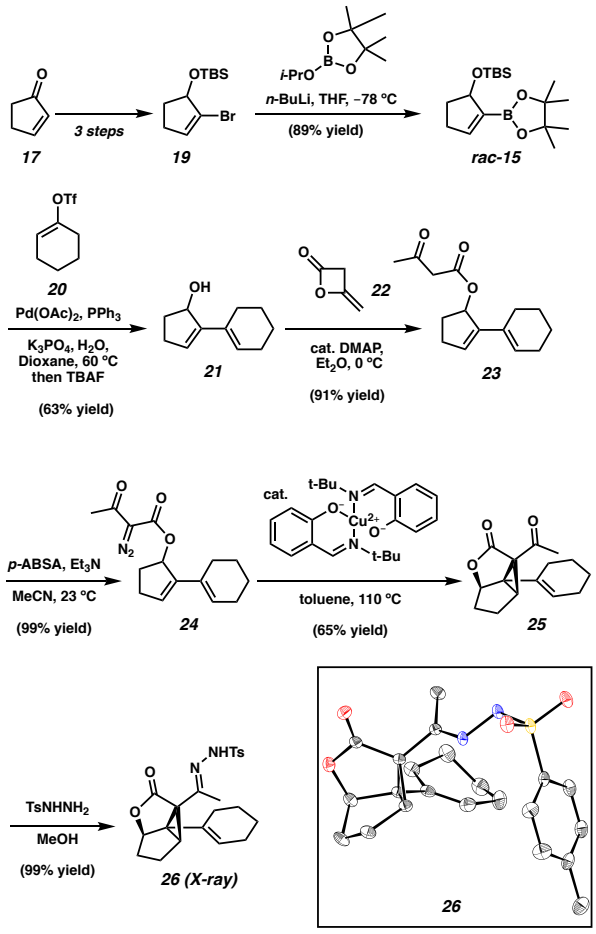


3.2. Model system approach and an unexpected rearrangement

Due to the complex structure of diazo ester **14**, we sought to first examine the cyclopropanation and divinylcyclopropane rearrangement sequence using model substrate **24**. Studies on this substrate could later be applied to limonene oxide (**18**) to accomplish the total synthesis.

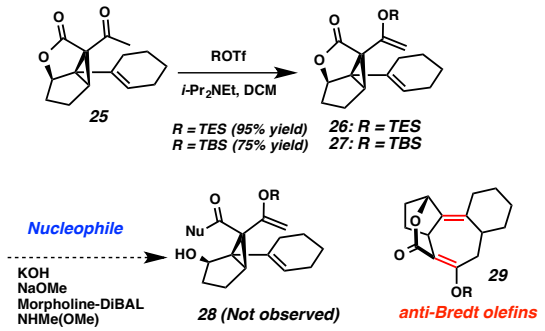
Investigation started with preparing model cyclopropanation precursor **24**. Diazo ester **24** was synthesized from allylic alcohol **21** via esterification with diketene (**22**) and a diazo transfer reaction. Allylic alcohol **21** was derived by Suzuki coupling of vinyl boronate *rac*-**15** and cyclohexanone triflate **20** followed by deprotection. Vinyl boronate *rac*-**15** was synthesized from known vinyl bromide **19**,[10] which was assembled by bromination, followed by Luche reduction and TBS protection from pentenone **17**. Subsequent cyclopropanation was affected by $Cu(TBS)_2$, and the desired cyclopropane **25** was observed in good yield. Cyclopropane **25** was easily converted to hydrazone **26**, of which we were able to confirm the structure from crystal X-ray diffraction (Scheme 2).

Scheme 2. Preparation of the Cyclopropane 25



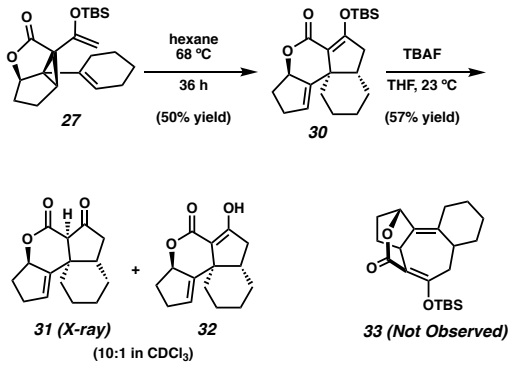
With cyclopropane **25** in hand, we directed our attention to the divinylcyclopropane rearrangement in order to construct the tricyclic system. We first investigated silyl enol ethers as the rearrangement precursor and divinylcyclopropanes **26** and **27** were prepared by silylation of ketone **25**. Divinylcyclopropanes **26** and **27** possessed a lactone moiety and would form two bridgehead olefins in **29** as a result of the divinylcyclopropane rearrangement. Thus, silyl enol ethers **25** and **26** were expected to have low reactivity. Several nucleophiles (KOH, NaOMe, Morpholine-DIBAL, Weinreb amine) were applied to release the lactone in order to initiate the rearrangement reaction; however all of our attempts were unsuccessful (Scheme 3).

Scheme 3. Lactone opening screen



Although divinylcyclopropane **27** was expected to show low reactivity due to its lactone moiety and formation of two potentially strained olefins (i.e., **33**), surprisingly it transformed to another silyl enol ether (i.e., **30**) under mild heating. Despite significant efforts, structural determination of silyl enol ether **30** proved difficult. Ultimately, the tetracyclic structure of β-ketolactone **31**, which was furnished by removing the TBS group, was confirmed by single crystal X-ray analysis (Scheme 4). In solution, β-ketolactone **31** was spectroscopically observed as a 10:1 mixture of keto/enol forms (i.e., **31** and **32**) by ^{1}H NMR.

Scheme 4. An unexpected rearrangement



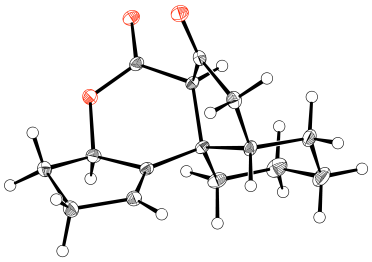
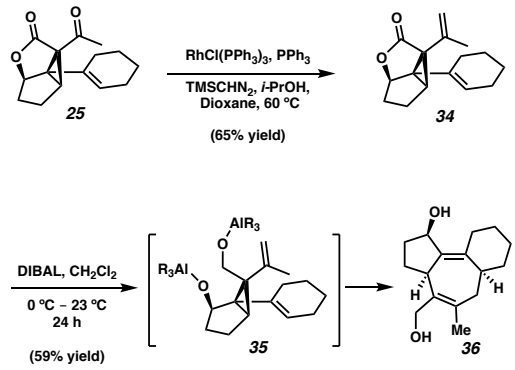


Figure 2. X-ray structure of unexpected *β*–ketolactone **31**.

We believed that ring strain from the lactone moiety prevented the formation of the desired tricyclic system. To overcome this obstacle, we imagined that the lactone moiety must first be ruptured. Since previous attempts with silyl enol ethers **26** and **27** were not satisfactory, we prepared divinylcyclopropane **34** via Wittig-type olefination using Wilkinson's catalyst and trimethylsilyl diazomethane as a methylene source.[11] The resulting divinylcyclopropane **34** was treated with DIBAL to reduce the lactone. Gratifyingly, reduction conditions also triggered the desired rearrangement, affording a tricyclic system **36**, likely via unstable bis-aluminum alkoxide intermediate **35** (Scheme 5).

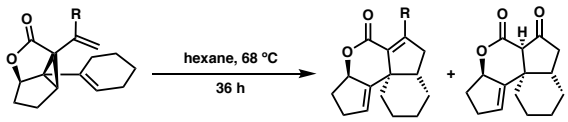
Scheme 5. Synthesis of tricyclic core 36



3.3. Mechanistic studies of the unexpected rearrangement

In order to gain greater insight into this unexpected rearrangement, we examined several divinylcyclopropanes (Table 1). The yield of the rearranged product is highest (57%) with a TES group, which undergoes complete desilylation (entry 1). The TIPS group remains intact after rearrangement, with a somewhat lower yield (39% yield, 20% recovered starting material, entry 3). In contrast, vinyl lactone **34** did not undergo the rearrangement to afford tetracycle (entry 4). Based on these results, we envisioned that the silyl enol ether moiety strongly affects or even participates in the transformation.

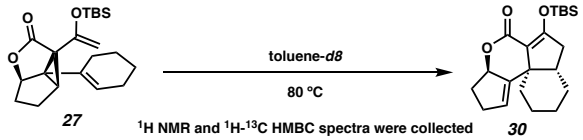
Table 1. The rearrangement of enol ethers.



entry	R	yield (%)	
1	–OTES	-	57
2	–OTBS	50	trace
3	–OTIPS	39	-
4	–Me	not observed	

We turned our attention to understanding the mechanism of the unexpected rearrangement giving rise to **30**. Thus, the rearrangement of **27** was repeated in toluene-*d8* and monitored by ^{1}H NMR (Scheme 6) and ^{1}H-^{13}C HMBC. While the NMR data showed smooth conversion to the rearranged product **30**, unfortunately no discernible intermediates were observed.

Scheme 6. NMR study



3.4. Computational studies

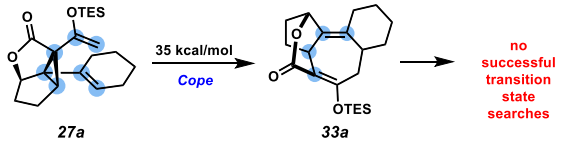
We undertook a computational study of the mechanism of the rearrangement using both the "trial-and-error" approach using standard transition-state search algorithms as implemented in Gaussian 09,[12] and automatic reaction path searches using single-component AFIR simulations for intramolecular

paths (SC-AFIR).[2d] In the latter method, reaction paths are explored automatically by applying an artificial force between pairs of reactive atoms. Details on this method are given in the Supporting Information. Here we describe how both methods identified the same mechanism for the rearrangement of **27** to form **30**.

The Morokuma group employed the single component SC-AFIR method as follows. Atoms that were deemed likely involved in the rearrangement were defined as reactive atoms. The AFIR algorithm simulates bond-formation by applying an artificial force between pairs of atoms, systematically evaluating all pairs of reactive atoms. In cases where the active atoms are initially bonded, a negative force can be applied to simulate bond-breaking. In this way, possible reaction paths were sampled using a relatively low level of theory (HF/3-21G) to allow for a large number of simulations. Energy maxima and minima were automatically optimized to locate transition states and intermediates, respectively.

Beginning with model **27a**, in which the TBS group was truncated to TES, the seven carbon atoms of the divinylcyclopropane moiety were defined as reactive atoms (Scheme 7, highlighted in blue). A large number of possible reaction pathways were found, but only the desired Cope rearrangement to **33a** had a low enough barrier to be feasible (35 kcal/mol, likely overestimated due to the low level of theory). Other reaction pathways included vinylcyclopropane rearrangements and hydrogen shifts with prohibitively high barriers (>60 kcal/mol, see Supporting Information). Subsequent rearrangement of **33a** was also simulated with the reactive atoms shown in Scheme 7, but no reasonable transition states could be located. These initial studies suggested that the desired Cope rearrangement was likely, but did not suggest a pathway to the observed product **30**. It was determined that other reactive atoms may be involved, which will be discussed later.

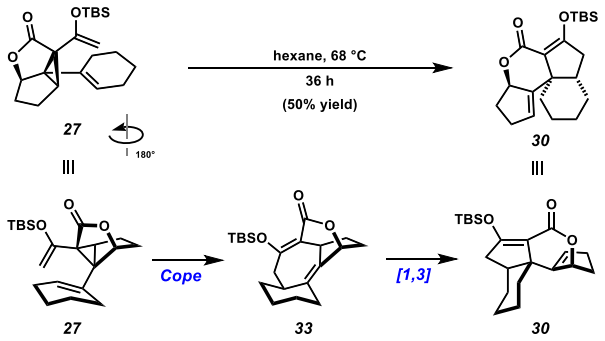
Scheme 7. Summary of initial AFIR simulations



While the AFIR studies were underway, the Houk group explored this mechanism by the more conventional "trial and error" approach, using density functional theory (DFT) calculations. Geometries were optimized using B3LYP/6-31G(d) in the gas phase. Single-point energy calculations were performed with the dispersion-corrected functional B3LYP-D3 using the larger 6-311++G(2d,2p) basis set and the IEF-PCM solvation model for *n*-hexane. The B3LYP functional was selected because it has been successfully used to study a number of diradical processes, and we suspected diradicals could be involved in the present rearrangement. We also computed single-point energies using M11-L and M06-2X. While the M06-2X functional has been shown to give accurate barriers and thermodynamics for pericyclic reactions,[13] it can give unreliable (overestimated) energies for diradical processes.[14] In contrast, M11-L is a local functional that has better performance for multi-reference systems, such as diradicals.[15,16] The ubiquitous functional B3LYP has also frequently been employed successfully in studies of radical processes.[17] In the current study, B3LYP-D3 and M11-L gave similar results, while M06-2X led to much higher energies for transition states with diradical character (see SI for details).

The hypothesis that directed the trial-and-error approach was that the desired Cope rearrangement of **27** occurs, but cycloheptadiene **33** is unstable due to the presence of two bridgehead double bonds in a 9-membered ring (Scheme 8). Further rearrangement occurs to alleviate strain, forming observed product **30** (along with desilylation to **31**). This rearrangement is formally a suprafacial 1,3-shift of the enol silane, which is disallowed by Woodward–Hoffmann rules. That is, the necessary 1r,3s sigmatropic shift is the only way that 33 could be transformed to 30, and this anti-aromatic cyclic 4 electron transition state or the diradical alternative were found to be prohibitively high in energy (see Figure 5 below). We therefore expected that a stepwise rearrangement would be the favored pathway, through either diradical intermediates or a series of pericyclic reactions. Although zwitterionic intermediates could also be proposed, these should be disfavored in nonpolar solvents.

Scheme 8. Mechanistic hypothesis



Our DFT study began by examining the Cope rearrangement of model compound **37**, in which the TBS group is replaced by TMS (Figure 3). The Cope rearrangement proceeds via boat-like **TS38**, which is very similar to prior computed Cope transition states of divinylcyclopropanes.[18] The free energy barrier is about 26 kcal/mol, which is reasonable for the reaction conditions but somewhat higher than Cope rearrangement of a simple divinylcyclopropane.[18] The reaction is endergonic by about 8 kcal/mol, despite the release of strain in the cyclopropane ring of **37**. A structural analysis of Cope product **39** shows the strain incurred by the two bridgehead alkenes (Figure 3, right). The alkenes are bent out of planarity, with C–C=C–C dihedral angles of 141 and 150 degrees, to accommodate the bicyclic system. The calculations predict that the Cope rearrangement can occur, but intermediate **39** is unstable and will either revert to **37** or undergo further rearrangement.

Experimentally, reduction of the ester in divinylcyclopropane **34** with DIBAL leads to spontaneous Cope rearrangement to cycloheptadiene **36**. We modeled this reaction using diol **40** as a model for the postulated aluminum alkoxide intermediate **35** (Figure 4). Cope rearrangement of **40** is exergonic by about 15 kcal/mol, with a free-energy barrier of about 19 kcal/mol. The stability of cycloheptadiene **36** relative to **39** highlights the torsional strain incurred by the two bridgehead double bonds in the 9-membered ring of **39**. Overall, these calculations are consistent with the hypothesis that bridging ester must be removed in order to forge the tricyclic core via a divinylcyclopropane rearrangement.

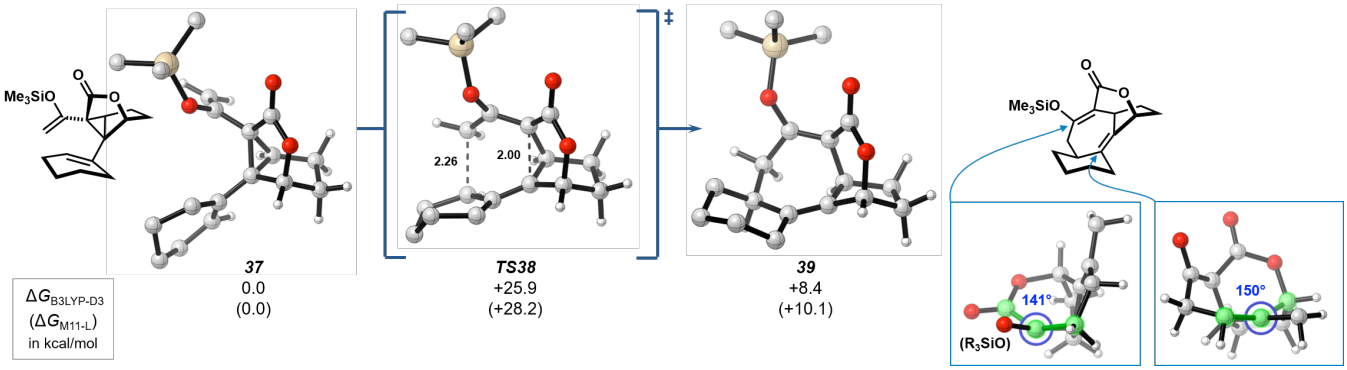


Figure 3. Cope rearrangement of divinylcyclopropane **37**

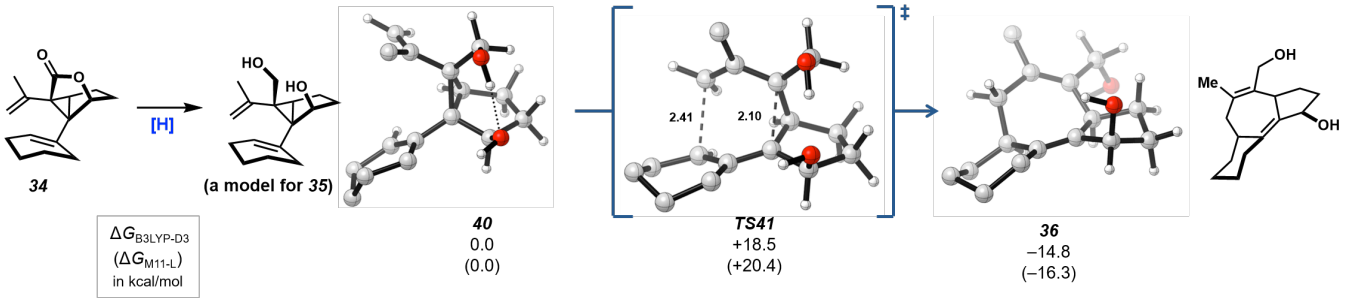
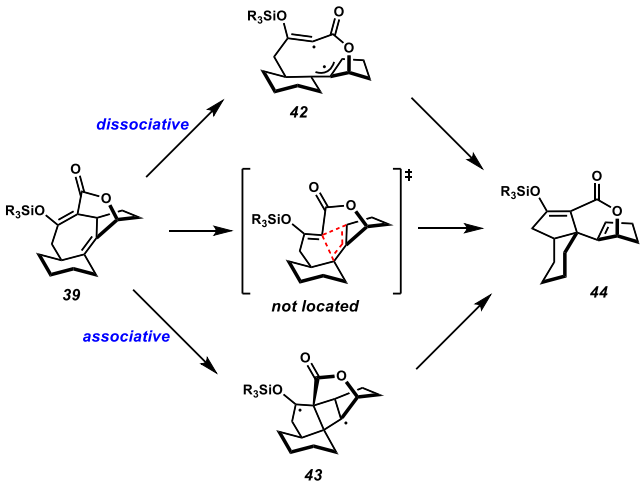


Figure 4. Computed structures for Cope rearrangement of reduced divinylcyclopropane **40**.

We next considered the possibility of a formal [1,3]-shift of the enol silane in **39** to form **44**, including the three limiting cases of concerted, dissociative, and associative processes (Scheme 9). We could not locate a transition state for the concerted process, which would violate Woodward–Hoffmann rules. The dissociative process involves C–C bond homolysis to generate the allylic/vinylic diradical **42**, while the associative process involves first C–C bond-formation to give the cyclobutylcarbinyl diradical **43**. Neither diradical could be located as a minimum using unrestricted DFT calculations.

Scheme 9. Possible mechanisms for formal 1,3-shift



In order to conclusively rule out diradical processes, we calculated the potential energy surface connecting the intermediate **39** to the product **44**. This surface involves breaking of C–C bond **a** and formation of C–C bond **b** (Figure 5). This analysis shows that a 70 kcal/mol barrier separates intermediate **39** from product **44**. Associative and dissociative processes are also ruled out, as the diradical intermediates **42** and **43** both appear on the potential energy surface at about 70 kcal/mol.

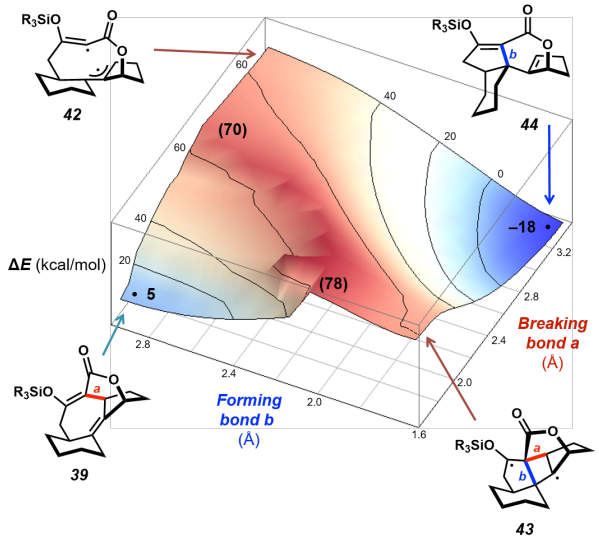


Figure 5. Potential energy surface directly connecting intermediates **39** and **44** calculated using UB3LYP/6-31G(d).

While the silyl protecting group remains intact in the observed product **44**, the experiments presented in Table 1 establish that a silyl group is crucial for the reaction. We therefore

considered participation of the silyl group in the rearrangement process. The 1,5-migration of silyl groups in protected 1,3-dicarbonyls has been reported to be rapid.[19] Our calculations indicate that 1,5-silyl migration in **39** occurs in a concerted manner via distorted square pyramidal transition state **TS45** (Figure 6). The formation of silyl ketene acetal **46** is endergonic with a barrier of 25.7 kcal/mol, making it competitive with the preceding Cope rearrangement.

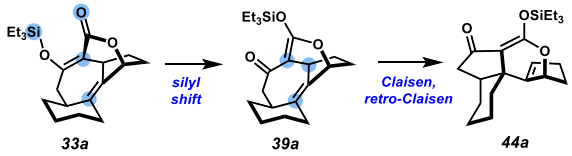
Silyl ketene acetal **46** is poised to undergo an Ireland–Claisen rearrangement to form the C–C bond (b) present in observed product **44**. The Claisen rearrangement is predicted to occur with a relatively low barrier of 20.3 kcal/mol to form alkylidene cyclobutane **48** (Figure 7). Transition state **TS47** corresponds to a concerted process, but has significant diradical character and is characterized by a very long breaking C–O bond. We were also able to locate a stepwise process leading through a diradical intermediate with a very similar barrier (within about 1 kcal/mol). The structures and energetics of this stepwise pathway are shown in the Supporting Information.

While alkylidene cyclobutane **48** is a relatively stable intermediate, it undergoes an unusually facile retro-Claisen rearrangement via **TS49** (14 kcal/mol). The formation of **50** is exergonic due to release of the significant strain associated with fused bicyclo[3.2.0]heptene system in **48**. Importantly, the Claisen/retro-Claisen sequence **46**→**50** represents a formal suprafacial 1,3-shift of the enol silane. A second 1,5-silyl shift affords the observed product **44**.

The free energy profile for the overall rearrangement of divinylcyclopropane **37** to give **44** is shown in Figure 8. The initial Cope rearrangement and 1,5-silyl migration have similar overall barriers of about 26 kcal/mol, while the Claisen/retro-Claisen steps have significantly lower barriers. Although the Cope rearrangement and [1,5]-silyl shift are endergonic, subsequent intermediates are significantly more stable due to a sequential release of strain. The Cope rearrangement is predicted to be rate-limiting such that no subsequent intermediates build up over the course of the reaction, consistent with experimental observations.

Amazingly, the Morokuma group arrived at the same conclusions at nearly the same time as the Houk group. After failing to find a pathway to **30** using the divinylcyclopropane moiety as reactive atoms, several silyl shifts were tested using the AFIR approach. From TES-protected **33a**, AFIR simulations led to **39a** via the same 1,5-silyl shift discussed above (Scheme 10, atoms circled in blue are defined as reactive atoms). From **39a**, with the three carbon atoms involved in the apparent 1,3-shift defined as reactive atoms, the Claisen/retro-Claisen sequence discussed above was also found from the AFIR simulations. A single AFIR simulation located both Claisen transition states and led to **44a**. In this case, the AFIR approach still required a chemist to define the correct target atoms before a reasonable pathway was found, and both AFIR and the "trial-and-error" approach independently converged to the same answer.

Scheme 10. AFIR simulations involving silyl migration



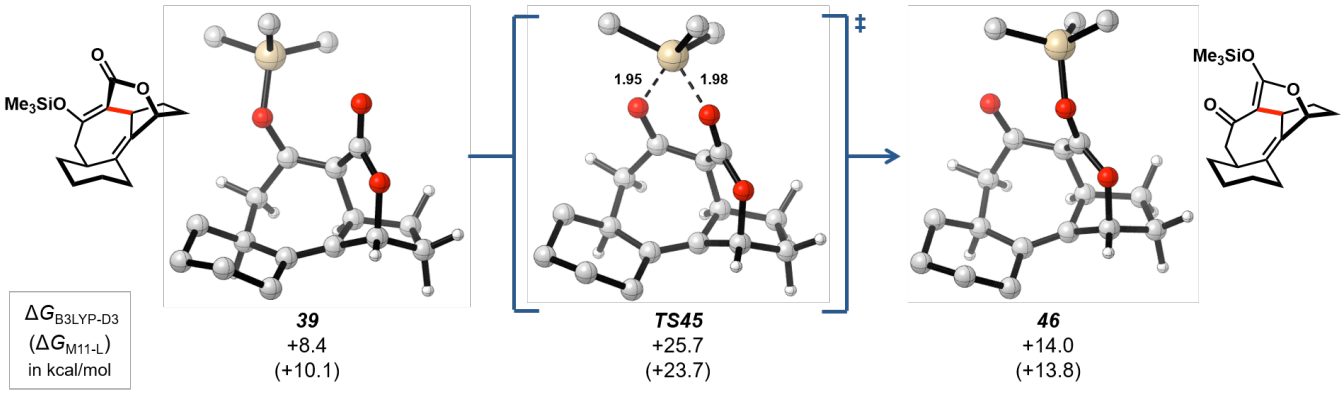


Figure 6. 1,5-silyl shift of enol silane **39**.

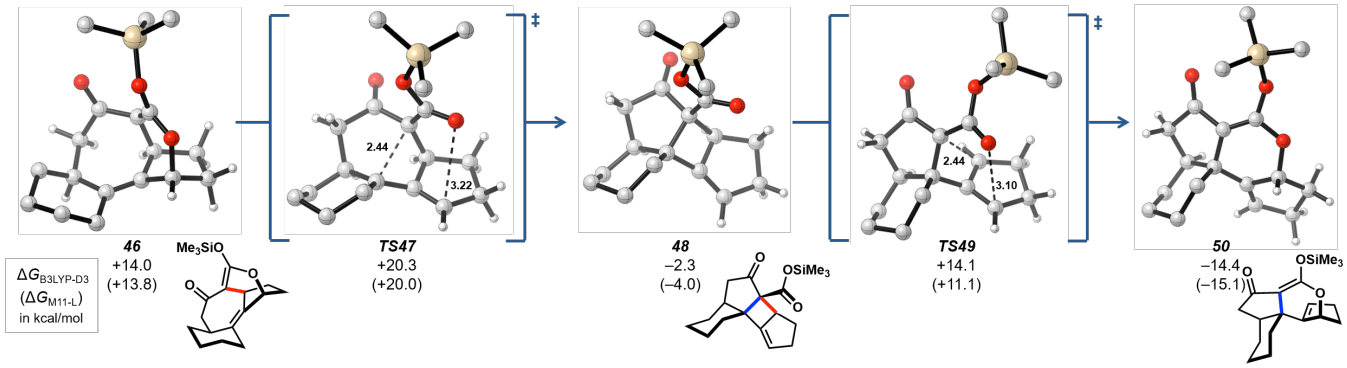


Figure 7. Formation and ring-opening of alkylidene cyclobutane **48**.

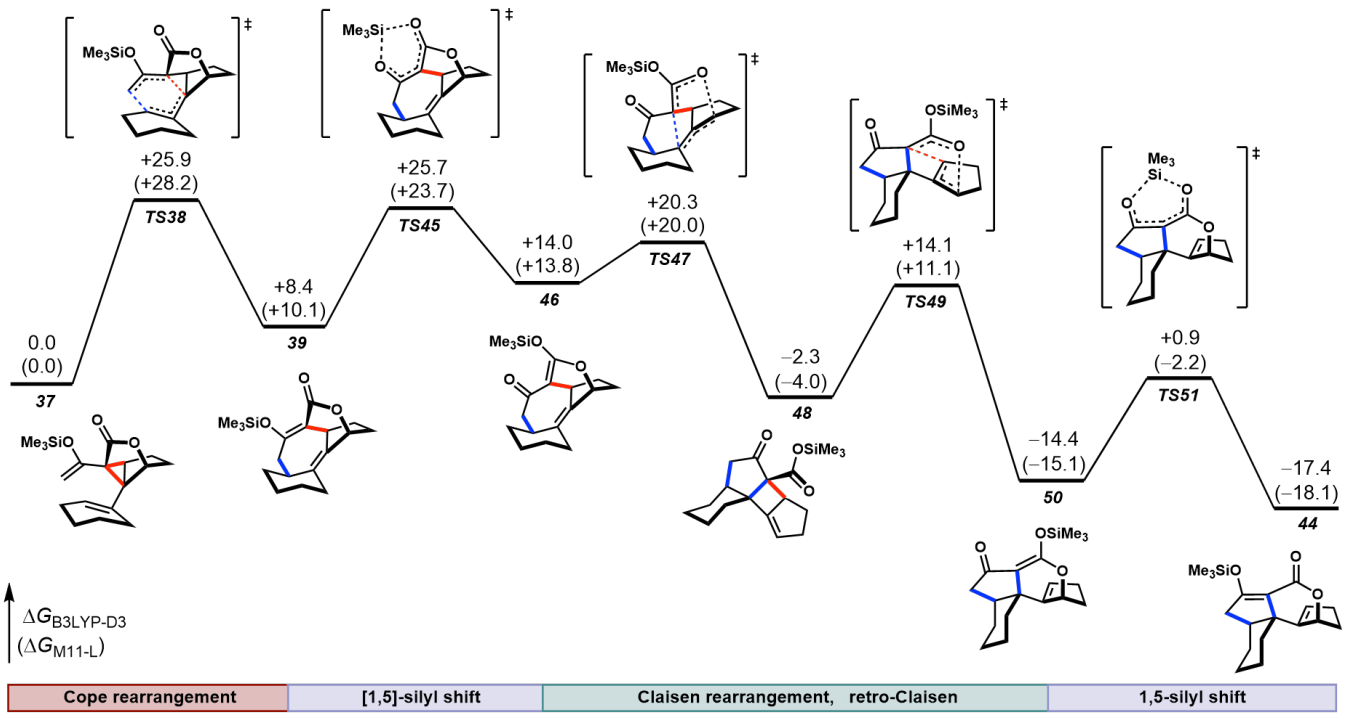


Figure 8. Free-energy profile for formation of **44** by a [1,5]-silyl shift/Claisen/retro-Claisen rearrangement cascade.

The alkylidene cyclobutane **48** represents a critical, and somewhat surprising intermediate in the Claisen/retro-Claisen sequence predicted by our DFT studies. Observation of **48** would provide conclusive validation of the proposed rearrangement cascade, but unfortunately **48** is predicted to undergo a very fast retro-Claisen rearrangement. As shown in Figure 9, the trisubstituted alkene in **48** (the experimental system) is distorted from planarity with a C–C=C–C dihedral angle of 146 degrees. This angle distortion in addition to the already strained fused cyclobutene illustrate why **48** is reactive enough to undergo a highly unusual retro-Claisen rearrangement.

Derivatives of **48** were investigated in hopes of finding a system where the alkylidene cyclobutane would be stable enough to be observable. Several derivatives are shown in Figure 9, along with with free energies computed with respect to the corresponding divinylcyclopropane **37**. Removal of the fused cyclohexane stabilizes cyclobutane **48b** slightly compared to **48**. However, removal of the two methylenes of the cyclopentene ring makes cyclobutanes **48c** and **48d** more stable by more than 10 kcal/mol. This modification removes the strain associated with the alkene, allowing C–C=C–C dihedral angles near 180 degrees. In addition, the ring system flattens out such that the alkene is no longer poised to engage the carbonyl in a retro-Claisen rearrangement. We were intrigued whether these derivatives would be stable enough to be observable or even isolable.

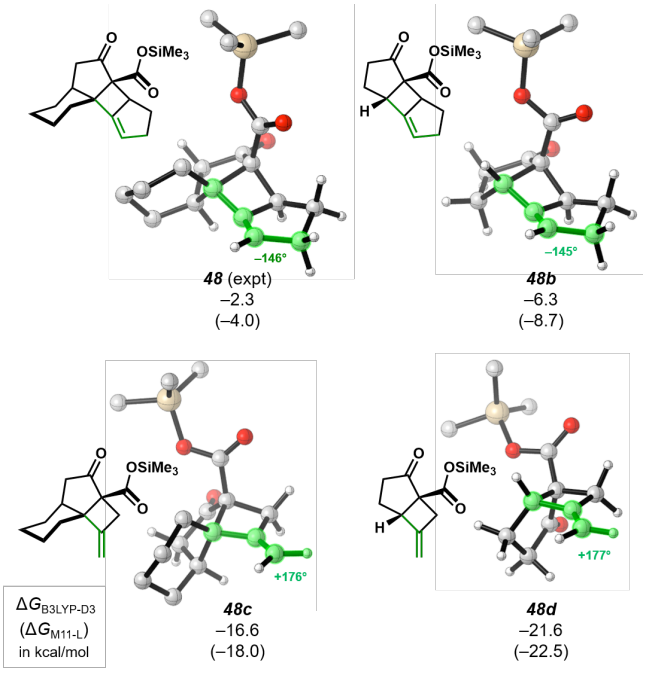
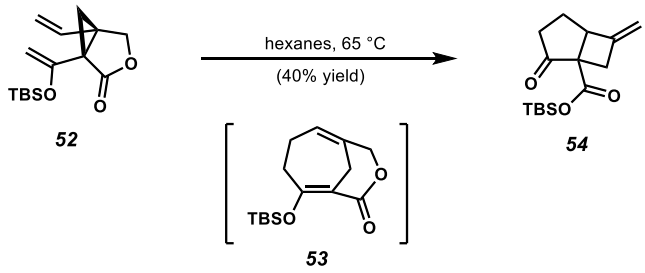


Figure 9. Stability of alkylidene cyclobutane **48** and derivatives.

The rearrangement cascade for the simplest (and most stable) methylidene cyclobutane **48d** was calculated to compare to the experimental system (Figure 10). The first three steps of the sequence (Cope rearrangement/[1,5]-silyl shift/ Claisen rearrangement) are very similar to the experimental system, with somewhat lower barriers. The formation of methylidene cyclobutane **48d** is predicted to be exergonic and irreversible. This is attributed to release of the strain associated with strained alkenes in **39d** and **46d** to form the relatively unstrained alkene in **48d**. Importantly, **48d** is predicted to be completely unreactive toward retro-Claisen rearrangement (**TS49d**), with a barrier of over 40 kcal/mol. Therefore, Cope rearrangement of **37d**, or other derivatives lacking the fused cyclopentane, is predicted to give **48d** as an observable product.

In fact, a thorough examination of the literature for related reactions revealed that this precise rearrangement was carried out by Davies and coworkers in 1997![20] Upon heating, divinylcyclopropane **52** (a TBS derivative of **37d**) undergoes rearrangement to methylidene cyclopropane **54** (Scheme 11). Though the mechanism was not known at the time, it was proposed to involve a Cope rearrangement to the desired but unobserved [4.3.1]-bicycle **53**, followed by further rearrangement. Amazingly, experimental validation of our computed mechanism was obtained 20 years ago.

Scheme 11. Rearrangement reported by Davies



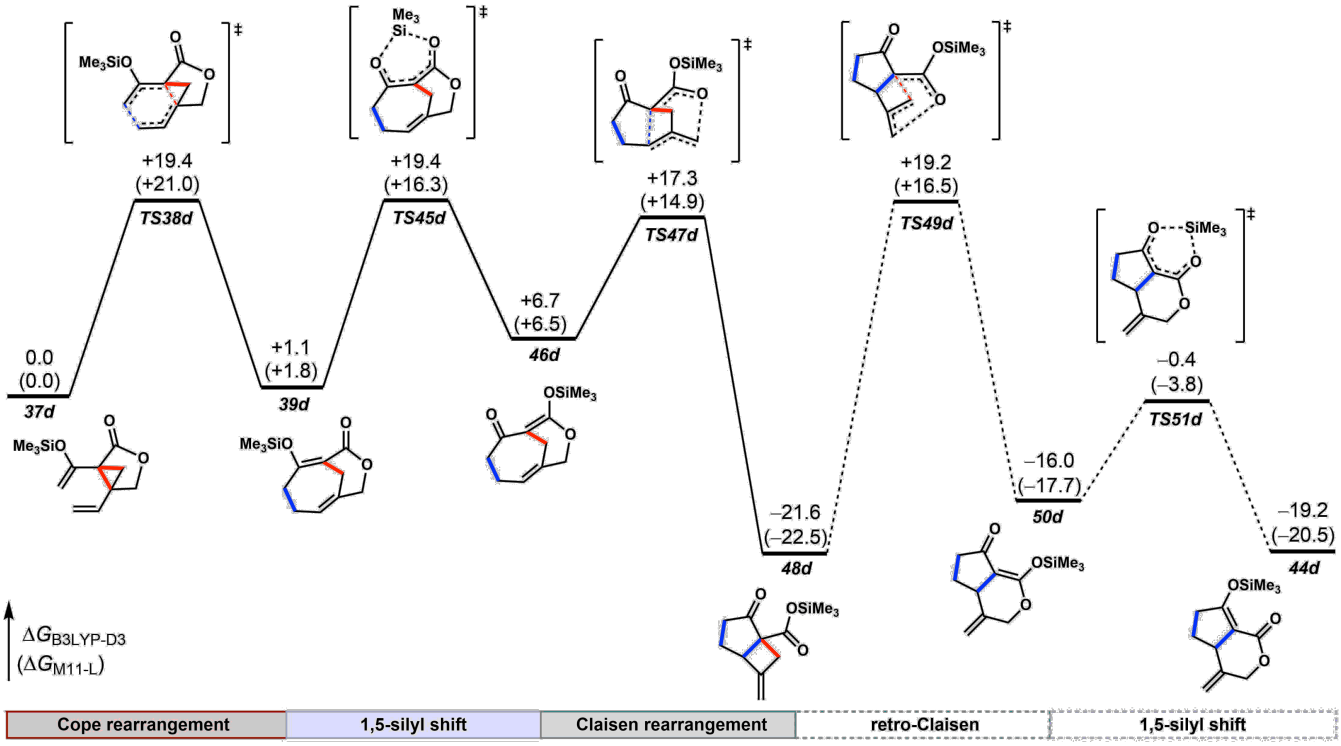


Figure 10. Free-energy surface for formation of alkylidene cyclobutane **48d**, which is unable to undergo further rearrangement.

4. Conclusion

In summary, a unique reaction cascade of divinylcyclopropanes containing silyloxy groups was computationally suggested, involving a quintet of five sequential thermally allowed sigmatropic shifts.[21] Both traditional "trial-and-error" and the automatic AFIR method were successful in predicting the same mechanism that has some precedent in the literature. Figure 8 summarizes this mechanism. Surprisingly, the cascade was found to include a cycloheptadiene intermediate with two bridgehead olefins via a [3,3]-Cope rearrangement. The intermediate was converted to the fused cyclobutane intermediate via a [1,5]-silyl shift followed by an Ireland–Claisen rearrangement. Finally, the tetracyclic compound was formed via a retro-Claisen rearrangement of the cyclobutane intermediate and subsequent [1,5]-silyl shift. Based on the mechanism and free-energy analysis, divinylcyclopropanes with a small-sized ring would result in unstable strained cyclobutane intermediates that should undergo a retro-Claisen/[1,5]-silyl shift sequence to afford tetracycles. In contrast, the rearrangement cascade of divinylcyclopropanes without fused carbocycles is expected to give a fused cyclobutane as an isolated product. This was observed in the earlier Davies work.[20] Computation has been found to be useful in the elucidation of a complex mechanism, and with current computer power, both the trial-and-error, and the automatic AFIR method were found to be similar effective in identifying a mechanism for this rearrangement. Details of the synthesis of Curcusone C will be reported from the Stoltz lab in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, single crystal X-ray analysis, detailed computational methods, Cartesian coordinates, and complete reference for Gaussian 09. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

stoltz@caltech.edu
houk@chem.ucla.edu

Present Addresses

‖ Corporate R&D, LG Chem, 188 Munji-ro, Yuseong-gu, Daejeon, 34122, Korea
▽ Department of Chemistry, University of Portland, 5000 N. Willamette Blvd., Portland, Oregon 97203
Department of Chemistry and Biochemistry, University of California at San Diego, La Jolla, California 92093

Author Contributions

§These authors contributed equally.

ACKNOWLEDGMENT

B.M.S. and C.W.L. thank NSF (CHE-1800511), Amgen, and Caltech for support of this research. K.N.H. thanks the NSF (CHE-1361104 and 1764238) for financial support of this research. B.L.H.T. gratefully acknowledges the National Institutes of Health for a postdoctoral fellowship (F32GM106596). Calculations were performed on the Hoffman2 Cluster at UCLA and the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by the NSF (OCI-1053575). The

authors thank Mr. Austin Wright (Caltech) for thoughtful comments about the manuscript.

DEDICATION

¶ Deceased, November 27, 2017

REFERENCES

1. Bachrach, S. M. *Computational Organic Chemistry*, **2007**, Hoboken, NJ, USA: John Wiley & Sons Inc.; *Encyclopedia of Computational Chemistry*, Schleyer, P. v. R., Ed., **1998**, Hoboken, NJ, USA: John Wiley & Sons Inc.

2. (a) Maeda, S.; Saito, R.; Morokuma, K. A systematic method for locating transition structures of A+B→X type reactions. *J. Chem. Phys.* **2010**, *132*, 241102/1–4. (b) Maeda, S.; Morokuma, K. Finding Reaction Pathways of Type A + B → X: Toward Systematic Prediction of Reaction Mechanisms. *J. Chem. Theo. Comp.* **2011**, *7*, 2335–2345. (c) Maeda, S.; Ohno, K.; Morokuma, K. Systematic exploration of the mechanism of chemical reactions: the global reaction route mapping (GRRM) strategy using the ADDF and AFIR methods. *Phys. Chem. Chem. Phys.* **2013**, *15*, 3683–3701. (d) Maeda, S.; Taketsugu, T.; Morokuma, K. Exploring transition state structures for intramolecular pathways by the artificial force induced reaction method. *J. Comp. Chem.* **2014**, *35*, 166–173. (e) Isegawa, M.; Maeda, S.; Tantillo, D. J., Morokuma, K. Predicting pathways for terpene formation from first principles – routes to known and new sesquiterpenes. *Chem. Sci.* **2014**, *5*, 1555–1560. (f) Ramozzi, R.; Morokuma, K. Revisiting the Passerini Reaction Mechanism: Existence of the Nitrilium, Organocatalysis of Its Formation, and Solvent Effect. *J. Org. Chem.* **2015**, *80*, 5652−5657. (g) Puripat, M.; Ramozzi, R.; Hatanaka, M.; Parasuk, W.; Parasuk, V.; Morokuma, K. The Biginelli Reaction Is a Urea-Catalyzed Organocatalytic Multicomponent Reaction. *J. Org. Chem.* **2015**, *80*, 6959−6967. (h) Sameera, W. M. C.; Maeda, S.; Morokuma, K. Computational Catalysis Using the Artificial Force Induced Reaction Method. *Acc. Chem. Res.* **2016**, *49*, 763−773.

3. Wang, L.-P.; Titov, A.; McGibbon, R.; Liu, F.; Pande, V. S.; Martinez, T. J. Discovering chemistry with an *ab initio* nanoreactor. *Nature Chem.* **2014**, *6*, 1044-1048.

4. Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. L. Transition Path Sampling: Throwing Ropes Over Rough Mountain Passes, in the Dark. *Ann. Rev. Phys. Chem.* **2002**, *53*, 291-318.

5. Jafari, M.; Zimmerman, P. M. Reliable and efficient reaction path and transition state finding for surface reactions with the growing string method. *J. Comp. Chem.* **2017**, *38*, 645-658.

6. (a) Bernauer, K.; Englert, G.; Vetter, W. An apocynaceae-alkaloid of a novel type. *Experientia* **1965**, *21*, 374–375. (b) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. Die Konstitution der *Melodinus*-Alkaloide (+)-Meloscin, (+)-Epimeloscin und (+)-Scandin. 1. Mitteilung über Alkaloide aus *Melodinus scandens* FORST. *Helv. Chim. Acta*. **1969**, *52*, 1886–1905. (c) Cannon, J. R.; Croft, K. D.; Matsuki, Y.; Patrick, V. A.; Toia, R. F.; White, A. H. Crystal structure and absolute configuration of (+)-scandine hydrobromide. *Aust. J. Chem.* **1982**, *35*, 1655–1664. (d) Openshaw, K. A review of *Jatropha curcas*: an oil plant of unfulfilled promise. *Biomass Bioenergy* **2000**, *19*, 1-15. (e) Szabó, L. F. Molecular interrelations in the *Melodinus* alkaloids. *ARKIVOC* **2007**, 280–290. (f) Fairless, D. Biofuel: The little shrub that could – maybe. *Nature* **2007**, *449*, 652.

7. (a) Naengchomnong, W.; Thebtaranonth, Y.; Wiriyachitra, P.; Okamoto, K. T.; Clardy, J. Isolation and structure determination of four novel diterpenes from jatropha curcus. *Tetrahedron Lett.* **1986**, *27*, 2439–2442. (b) Chianese, G.; Fattorusso, E.; Aiyelaagbe, O. O.; Luciano, P.; Schröder, H. C.; Müller, W. E. G.; Taglialatela-Scafati, O. Spirocurcasone, a Diterpenoid with a Novel Carbon Skeleton from *Jatropha curcas*. *Org. Lett.* **2011**, *13*, 316–319. (c) Liu, J.-Q.; Yang, Y.-F.; Li, X.-Y.; Liu, E.-Q.; Li, Z.-R.; Zhou, L.; Li, Y.; Qiu, M.-H. Cytotoxicity of naturally occurring rhamnofolane diterpenes from Jatropha curcas. *Phytochemistry* **2013**, *96*, 265–272. (d) Zhu, Q. A., J.; Li, F.; Wang, M.; Wu, J.; Tang, Y. *Chin.* Curcusone C Induces Apoptosis in Human Ovarian Cancer SK-OV-3 Cells. *J. Appl. Environ. Biol.* **2013**, *19*, 956–959. (e) Li, Y.; Dai, M. Total Syntheses of the Reported Structures of Curcusones I and J through Tandem Gold Catalysis. *Angew. Chem. Int. Ed.* **2017**, *56*, 11624–11627.

8. Mayasundari, A.; Young, D. G. J. Silicon-tethered Heck reaction. *Tetrahedron Lett.* **2001**, *42*, 203-206.

9. Khan, S.; Nobuki, K.; Masahiro, H. Stereoselective Synthesis of Functionalized (*Z*)-Keto-enyne and its Epoxide. *Synlett* **2000**, 1494–1496.

10. Wang, Q.; Fan, S. Y.; Wong, H. N. C. Enantioselective synthesis of chiral liquid crystalline compounds from monoterpenes. *Tetrahedron* **1993**, *49*, 619–638.

11. Lebel, H.; Paquet. V. Rhodium-Catalyzed Methylenation of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 320–326.

12. Frisch, M. J.; et al. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.

13. Pieniazek, S. N.; Clemente, F. R.; Houk, K. N. Sources of Error in DFT Computations of C–C Bond Formation Thermochemistries: π→σ Transformations and Error Cancellation by DFT Methods. *Angew. Chem. Int. Ed.* **2008**, *47*, 7746–7749.

14. James, N. C.; Um, J. M.; Padias, A. B.; Hall Jr., H. K.; Houk, K. N. Computational Investigation of the Competition between the Concerted Diels–Alder Reaction and Formation of Diradicals in Reactions of Acrylonitrile with Nonpolar Dienes. *J. Org. Chem.* **2013**, *78*, 6582−6592.

15. (a) Peverati, R.; Truhlar, D. G. M11-L: A Local Density Functional That Provides Improved Accuracy for Electronic Structure Calculations in Chemistry and Physics. *J. Phys. Chem. Lett.* **2012**, *3*, 117−124. (b) Peverati, R.; Truhlar, D. G. Quest for a universal density functional: the accuracy of density functionals across a broad spectrum of databases in chemistry and physics. *Phil. Trans. R. Soc. A* **2014**, *372*, 20120476.

16. Kedziora, G. S.; Barr, S. A.; Berry, R.; Moller, J. C.; Breitzman, T. D. Bond breaking in stretched molecules: multi-reference methods versus density functional theory. *Theor. Chem. Acc.* **2016**, *135*, 79.

17. (a) Zhao, Y.-L.; Suhrada, C. P.; Jung, M. E.; Houk, K. N. Theoretical Investigation of the Stereoselective Stepwise Cope Rearrangement of a 3-Vinylmethylenecyclobutane. *J. Am. Chem. Soc.* **2006**, *128*, 11106–11113. (b) Leach, A. G.; Houk, K. N. The mechanism and regioselectivity of the ene reac-

tions of nitroso compounds: a theoretical study of reactivity, regioselectivity, and kinetic isotope effects establishes a stepwise path involving polarized diradical intermediates. *Org. Biomol. Chem.* **2003**, *1*, 1389–1403. (c) Gräfenstein, J.; Hjerpe, A. M.; Kraka, E.; Cremer, D. An Accurate Description of the Bergman Reaction Using Restricted and Unrestricted DFT: Stability Test, Spin Density, and On-Top Pair Density. *J. Phys. Chem. A* **2000**, *104*, 1748–1761.

18. (a) Su, J. T.; Sarpong, R.; Stoltz, B. M.; Goddard W. A. Substituent Effects and Nearly Degenerate Transition States: Rational Design of Substrates for the Tandem Wolff−Cope Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 24–25. (b) Özkan, İ.; Zora, M. Transition Structures, Energetics, and Secondary Kinetic Isotope Effects for Cope Rearrangements of *cis*-1,2-Divinylcyclobutane and *cis*-1,2-Divinylcyclopropane: A DFT Study. *J. Org. Chem.* **2003**, *68*, 9635–9642. (c) Krüger, S.; Gaich, T. Recent applications of the divinylcyclopropane–cycloheptadiene rearrangement in organic synthesis. *Beilstein J. Org. Chem.* **2014**, *10*, 163–193.

19. McClarin, J. A.; Schwartz, A.; Pinnavaia, T. J. 1,5-Migrations of silicon between oxygen centers in silyl β-diketones**.** *J. Organomet. Chem.* **1980**, *188*, 129–139.

20. (a) Davies, H. M. L.; Calvo, R.; Ahmed, G. Type II intramolecular annulations between vinylcarbenoids and furans. *Tetrahedron Lett.* **1997**, *38*, 1737–1740. (b) Davies, H. M. L.; Calvo, R.; Townsend, R. J.; Ren, P.; Churchill, R. M. An Exploratory Study of Type II [3 + 4] Cycloadditions between Vinylcarbenoids and Dienes. *J. Org. Chem.* **2000**, *65*, 4261–4268.

21. Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. Toward a Symphony of Reactivity. Cascades Involving Catalysis and Sigmatropic Rearrangements. *Angew. Chem. Int. Ed.* **2014**, *53*, 2556–2591.

TOC Graphic