Title

Construction of Seven-Membered Oxacycles Using a Rh(I)-Catalyzed Cascade C—C Formation/Cleavage of Cyclobutenol Derivatives

Journal

The Journal of Organic Chemistry, 89(7)

ISSN

0022-3263

Authors

Ham, Jin Su

Son, Mina

Na, Christina G

et al.

Publication Date

2024-04-05

DOI

10.1021/acs.joc.3c02914

Peer reviewed

HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2024 December 15.

Published in final edited form as:

J Org Chem. 2024 April 05; 89(7): 4647–4656. doi:10.1021/acs.joc.3c02914.

Construction of Seven-Membered Oxacycles Using a Rh(I)-Catalyzed Cascade C–C Formation/Cleavage of Cyclobutenol Derivatives

Jin Su Ham,
Department of Chemistry, University of California, Berkeley, California 94720, United States

Mina Son,
Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea

Christina G. Na,
Department of Chemistry, University of California, Berkeley, California 94720, United States

Bohyun Park,
Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

Mu-Hyun Baik,
Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

Richmond Sarpong
Department of Chemistry, University of California, Berkeley, California 94720, United States

Corresponding Authors: Mu-Hyun Baik – Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Republic of Korea; Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea; mbaik2805@kaist.ac.kr, Richmond Sarpong – Department of Chemistry, University of California, Berkeley, California 94720, United States; rsarpong@berkeley.edu.

The authors declare no competing financial interest.

ASSOCIATED CONTENT

***sı Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c02914.

Experimental procedures, characterization data, NMR spectra, details of DFT calculations, and X-ray data for **6a**,*epi*-**6a**, **15**, *epi*-**6s**, and **28** PDF

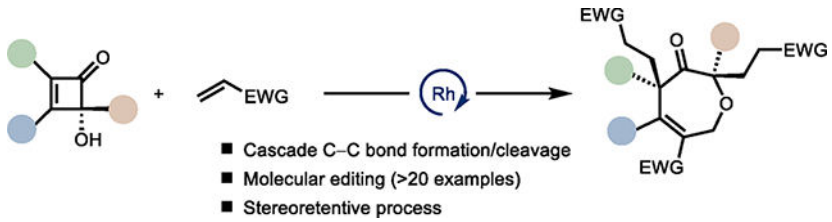
Accession Codes

CCDC 2169148 and 2213191–2213194 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

Abstract

Herein, we describe the synthesis of substituted oxepane derivatives through the skeletal remodeling of 4-hydroxy-2-cyclobutenones, which are readily prepared from commercially available dialkyl squarates upon their reaction with acrylonitrile. Mechanistically, a Rh(I)-catalyzed C–C bond formation and cleavage cascade is proposed. Specifically, a fused [3.2.0] bicycle is proposed to form from dialkyl squarate-derived cyclobutenols via an unusual Rh(I)-catalyzed intermolecular oxa-Michael addition of a tertiary alcohol with acrylonitrile, followed by an intramolecular conjugate addition/migratory insertion. Subsequent $C(sp^3)$–$C(sp^3)$ bond cleavage through a Rh-catalyzed β-carbon elimination is then theorized to furnish the oxepane scaffold. Computational studies support the formation of an intermediate [3.2.0] bicycle but also point to an alternative pathway for the formation of the oxepane products involving a Rh(III) intermediate. Additional studies have shown the overall process to be stereoretentive. The functional groups that are introduced in this process can be leveraged to form fused or bridged ring systems.

Graphical Abstract



INTRODUCTION

The oxepane moiety is a structural motif that is found in natural products, including those isolated from marine invertebrates such as mollusks, sponges, algae, and marine fungi (Figure 1).[1] Because of the diverse biological properties of oxepane-containing molecules, including anticancer, antibacterial, and antifungal activities, synthetic strategies and methods for preparing these seven-membered cyclic ethers continue to be sought.[2] However, the relatively high enthalpic and entropic barriers associated with the syntheses of these medium-sized cyclic ethers through ring closure[3] have made this a challenging endeavor – especially when compared to the methods available for the syntheses of either five- or six-membered cyclic ethers.

Broadly, strategies for building seven-membered cyclic ethers have included direct cyclization[4] and ring expansion involving three-membered rings such as cyclopropanes or epoxides.[2g,5] Six-membered vinyl cycloalkanols[6] or cyclohexanones[7] have also been employed to construct the oxepane core through one-atom ring expansion. Notably, there are no reported examples using four-membered carbocycles as precursors to seven-membered oxacycles.

As part of our group's ongoing interest in devising C–C bond cleaving methods to access unique scaffolds, we envisioned an approach to the oxepane scaffold using squaric acid derivative—specifically, 4-hydroxy-2-cyclobutenones, which can be readily prepared

from organolithium addition to commercially available dialkyl squarates. Owing to their inherent ring-strain and reactive enone moiety, cyclobutenones have served for almost a century as valuable building blocks in chemical synthesis.[8] The use of squaric acid derivatives as substrates can be categorized into four major reaction manifolds (Scheme 1). The 4π electrocyclic ring opening of squaric acid derivatives to generate reactive ketene intermediates under photochemical or thermal conditions[9] is perhaps the best known of these transformations. Diels–Alder cycloadditions of squarate derivatives with dienes, driven by the release in ring strain, to provide fused cyclohexene products[10] have also been reported. 1,2- and 1,4-additions have also been investigated using various nucleophiles.[9,11] More recently, reactions involving transition metal-catalyzed C–C bond cleavage to provide either five- or four-membered metallocycles (following decarbonylation) that can be engaged in subsequent [4 + 2] or [3 + 2] cycloadditions have been reported.[8,12]

We hypothesized that an alternative transformation of 4-hydroxy-2-cyclobutenones (**1**, Figure 2) could be realized through transition-metal-catalyzed C–C bond cleavage by leveraging both the peripheral hydroxy functional group and the enone double bond of the cyclobutenone system. Specifically, we theorized that the hydroxy group of **1** could undergo an oxa-Michael addition in the presence of an electron-deficient electrophile to provide adduct **2,** which would undergo an intramolecular conjugate addition or migratory insertion into the enone moiety to provide fused [3.2.0] bicycle **3**. Subsequent C–C bond cleavage through β-carbon elimination would then furnish the oxepane scaffold (**3** → **4**, Figure 2) poised for further reactivity of the metal enolate. Overall, this skeletal framework remodeling approach would provide access to a diverse array of oxepane-derived products from 4-hydroxy-2-cyclobutenones.

RESULTS AND DISCUSSION

Reaction Discovery and Optimization.

We commenced our studies using cyclobutenol **1a** (Table 1), which was easily prepared by 1,2-addition of phenyllithium into dimethyl squarate. Several challenges were anticipated with our proposed transformation. Specifically, oxa-Michael reactions are not general because of their reversibility – as evidenced by the lack of precedent for the conjugate addition of tertiary alcohols to electron-deficient alkenes.[13]

In a reaction of **1a** with $[Rh(cod)(OH)]_2$, Xantphos, and excess acrylonitrile[14] at 100 °C (Table 1, entry 1), the desired oxepane derivative **6a** was observed, albeit in low yield along with a significant amount of enone 5. This enone side product presumably arises from a β-carbon elimination from a Rhalkoxide generated from 1a that undergoes cleavage of the C–C bond distal to the alkene prior to oxa-Michael addition followed by protodecarbonylation.[15] We observed higher yields of 6a at lower temperatures (entries 2–4), with the highest yield observed at 40 °C (61% yield, entry 3). Remarkably, reaction at room temperature resulted in only slightly diminished yields (51% yield, entry 4). Control experiments revealed the importance of both the Rh precatalyst as well as the ligand, as no reaction was observed in the absence of either component (entries 5, 6, and 8). Interestingly, the reaction did proceed in the absence of base, providing **6a** in only slightly lower yield

(56% yield, entry 7). Lower yields were also observed when 1,4-dioxane was used as the solvent instead of toluene (entry 9) or at higher concentrations (entry 10).

With the exception of $[Rh(cod)(OMe)]_2$ (Table 2, entry 2), no reaction was observed with other Rh(I), Rh(II), or Rh(III) complexes (Table 2), pointing to the importance of not only the oxidation state of Rh to the reaction but also the identity of the X-type ligand on the starting Rh complex.

After screening various ligands, we found that, with few exceptions, most other ligands, including other bidentate phosphine and Buchwald-type ligands, did not lead to product formation (Table 3, entries 2–8). On the basis of the relative success we encountered with Xantphos, we screened other Xantphos-type ligands (entries 9–11). Overall, we found that the more electron-rich Cy-Xantphos and DEA-Xantphos ligands provided a modest increase in yield. The addition of one equivalent of anhydrous Na_2SO_4 further increased the yield to provide the desired product in 80% yield (entry 11). This latter observation suggested that water adversely affects reaction progress, and therefore, the use of a drying agent is important for obtaining high yields (see the Supporting Information for a more comprehensive base and drying agent screen). When ^{t}Bu-Xantphos, which has the largest bite angle of the Xantphos-type ligands we investigated, was employed as a ligand, only the *O*-alkylation product (7) and the starting material (**1a**) were obtained, indicating that the proposed migratory insertion into the enone moiety of the cyclobutenone may be challenging in this case due to the increased steric repulsion around the metal center.

Different side products, such as fused [3.2.0] bicycle **8**, the result of 1,4-addition of Rh species **3** (see Scheme 2a) into acrylonitrile, were observed when cataCXium A was used as the ligand. Furthermore, *5H*-furanone **9** was obtained, presumably through a Rh-catalyzed β-carbon elimination and subsequent isomerization (see Scheme 3) rather than through the well-established 4π electrocyclic ring opening of cyclobutenones.[9f] Differences in reactivity imparted by the ligands became more pronounced when the reactions were carried out in the absence of acrylonitrile (Scheme 2b). For example, only isomerization of **1a** to **10** was observed when cataCXium A was used as the ligand. However, when DEA-Xantphos was used as a ligand, mostly unreacted 1a was recovered along with a relatively small amount of butenolide **10**.

Scope of Oxepane Scaffold Formation.

With the optimized conditions in hand, we investigated the scope of the Rh(I)-catalyzed formation of oxepane derivatives from α-hydroxy cyclobutenones (Table 4). Substrates with various aromatic groups were prepared first to probe the effect of varying the electronics on the arene. With electron-donating substituents on the arene, such as methyl (**6b, 6c**), methoxy (**6e**), alkylthio (**6f**), trimethylsilyl (**6i**), and alkynyl (**6j**) functionalities, moderate to good yields of the oxepane-based products were obtained. Electron-withdrawing groups such as trifluoromethyl (**6d**) and various halides (**6g, 6h**) also had minimal influence on the efficiency of the Rh-catalyzed ring expansion, with the corresponding oxepane-type products isolated in comparable yield. The aryl chloride functional group (**6h**) presents opportunities for further functionalization through subsequent cross-coupling reactions. The oxepane-forming reaction also tolerated a wide range of heterocycles, including thiophene

(**6k**), furan (**6l**), benzofuran (**6m**), isoquinoline (**6o**), and indole (**6p**). However, the yield resulting from an isoquinoline-containing substrate was low (see **6o**), most likely due to the strong binding of the nitrogen lone pair to the metal center, which impedes the transformation. Finally, alkyne-substituted oxepane derivative **6q** could also be prepared through the Rh(I)-catalyzed cascade reaction.

Interestingly, in the case of 2-pyridyl bearing cyclobutyl alcohol **1r** (Scheme 3), we observed butenolide **14** as the sole product. We propose that in this case (as in the formation of **11**), the pyridine nitrogen lone-pair directly binds the acyl rhodium intermediate, likely preventing the oxa-Michael addition that would lead to the oxepane core. Instead (see **11** → **13**), isomerization via ketene intermediates ultimately leads to butenolide derivative **14** following a terminating addition of the Rh-enolate into acrylonitrile. Alternatively, migratory insertion of acyl-Rh intermediate **11** into the carbonyl group[16] will lead to the same organo-Rh intermediate that can be accessed from **13** en route to **14.**

We have also investigated the substrate scope with respect to different C1 and C2 substituents on the α-hydroxy-cyclobutenone core of the starting material (Table 5). Changing the methoxy groups to ethoxy or isopropoxy yielded products **6r** and **6s**, which were each accompanied by fused [3.2.0] bicyclic compounds **15** and **16**, respectively. It appears that increasing the size of the alkoxy groups in these cases slows the rate of the proposed β-carbon elimination (i.e., from the metal enolate intermediates corresponding to **3**, Figure 2). As a result, 1,4-addition with acrylonitrile occurs competitively with the 4,5-fused bicyclic metal enolate intermediate to give **15** or **16.** We observed the epimeric 1,4-adduct (see **6s**) as the major product from the isopropoxy-substituted substrate. In this case, we propose that the developing stereocenter resulting from acrylonitrile addition is dictated by the larger O^{i}Pr group adopting a disposition to avoid a steric clash with the phenyl group from the resident stereocenter. Alkyl substituents in place of the alkoxy groups also yielded competent substrates for oxacycle synthesis (**6t–6v**).

Mechanistic Studies and Diversification of the Oxepane-Based Products.

We performed additional studies to gain insight into the mechanism of the reaction (Scheme 4). First, we demonstrated that the first conjugate addition is not merely a base-promoted process. Oxa-Michael products (**7** or **18**) were not observed from either hydroxycyclobutenone **1a** (Scheme 4a) or cyclobutanol **17** (Scheme 4b) using conditions typically employed in oxa-Michael additions (e.g., with potassium *tert*-butoxide).[13g] However, applying our standard conditions provided the desired *O*-alkylation of **17** to form **18** in good yield. This result suggests that the Rh alkoxide is critical for oxa-Michael addition.

In addition, we found that the reaction was sensitive to the steric environment of the substrate. For example, using *tert*-butyl adduct **1x** (Scheme 5a) as a substrate, only the starting material was recovered. In this case, it is likely that *O*-alkylation did not occur due to the high steric demand associated with Rh alkoxide formation. With *tert*-butoxy groups at C1 and C2, only the oxa-Michael adduct (**19**) formed, demonstrating that migratory insertion into the cyclobutenone is heavily influenced by the steric environment around C2

(Scheme 5b). Indirect evidence for the generation of the ring-expansion intermediate (i.e., **4**; see Figure 2) could be found by using vinyl-substituted substrate **1z** (Scheme 5c). Exo-olefin **22** was isolated along with *O*-alkylation adduct **20** and oxepane derivative **21** under the reaction conditions, supporting the likely intermediacy of an η^3 adduct (see 23) from the α-alkyl rhodium intermediate. Reaction using enantioenriched **1u** (99% ee) provided **6t** in 92% ee, showing that the overall transformation has a high level of chirality transfer (Scheme 5d).

Resubjecting either **6a** or *epi*-**6a** to the reaction conditions did not lead to epimerization, indicating that the C–C bond-forming conjugate additions to acrylonitrile are likely irreversible under the reaction conditions (Scheme 6).

To gain insight into the proposed mechanism and feasibility of the outlined transformations, a detailed computational study based on density functional theory (DFT)[17] was conducted, as described in Figure 3, with Xantphos as the model ligand. First, a pathway involving the experimentally observed [3.2.0] intermediate was explored. As previously described,[15] the reaction is likely initiated by the deprotonation of cyclobutanol **1a** by the Rh–OH complex (Figure S1, **A1**), releasing water as the byproduct and forming intermediate **A4**. This step is calculated to be very facile and has an estimated barrier of only 1.7 kcal/mol. The envisioned oxa-Michael addition is calculated to proceed via **A4-TS** at 18.4 kcal/mol and should also readily occur under the reaction conditions.

In order to form the [3.2.0] intermediate, **A5** was calculated to rearrange to **A5′** via six-membered metallacyclic transition state **A5-TS′** (barrier of 25.4 kcal/mol) to first form the [3.2.0] intermediate scaffold in **B1**. If the reaction were to proceed directly from **A5**, a four-membered transition state with a high barrier of 44.0 kcal/mol would be required (Figure S2, **A5-TS″**). Therefore, the nitrile group of acrylonitrile and the methoxy group of squaric acid are both important for the success of this reaction. While formation of the [3.2.0] fused-ring intermediate has a plausible calculated barrier, calculations show that the subsequent C–C bond cleavage has an associated transition state, **B4-TS**, that has a prohibitively high barrier of 36.3 kcal/mol.

Therefore, we explored an alternative pathway from **A5.** The C–C bond of the squarate moiety can be oxidatively cleaved via **A5-TS** located at 26.0 kcal/mol, forming Rh(III) intermediate **A6**.[18] Reductive elimination via **A6-TS**, should result in the Rh(I) oxidation state, forming the oxepane-based scaffold in **A7**. Notably, **A5-TS** and **A5-TS′** are practically isoenergetic at 26.0 and 25.4 kcal/mol, respectively, implying that both transformations are possible and that the [3.2.0] intermediate from **B1** can readily be accessed. When we compare the overall barrier of the two pathways, however, the barrier associated with the Rh(III) intermediate is 32.0 kcal/mol, whereas the barrier associated with the pathway involving the [3.2.0] intermediate is 36.3 kcal/mol. Thus, calculations suggest that the experimentally observed [3.2.0] intermediate might be an intermediate of an unproductive side pathway that does not lead to the final product. Other pathways, such as a conrotatory 4π electrocyclic ring-opening of Rh-enolate intermediates such as **B3** are not possible because of the unfavorable geometry of the resulting double bonds in the seven-membered ring (Figure S4). Thus, although the barrier of 32.0 kcal/mol seems somewhat high, given

the experimental conditions, the suggested mechanism was found to be the lowest path that could be obtained from the DFT calculations.

We also investigated diversifying the oxepane derivatives accessible using this method by leveraging the rich functionalities present in these products (Scheme 7). For instance, the primary nitrile groups can be easily converted into esters (see oxepane **24**) using trimethylsilyl chloride in a Pinner reaction (Scheme 7a).[13d] Hydride reduction of **6a** proceeded smoothly to furnish alcohol **25** as a single diastereomer, which upon esterification gave acetate **26** in good yield (Scheme 7b). Starting from *epi*-**6a**, diastereoselective hydride reduction and chain-end ester formation provided **28,** which participated in an acid-catalyzed lactonization to form fused lactone **29** (Scheme 7c). Finally, allylic bromination with concomitant nucleophilic engagement by the methoxy group provided the [3.2.1] bridged compound **30** in a single step (Scheme 7d).

CONCLUSIONS

In summary, we report a new approach for the synthesis of seven-membered oxepane derivatives starting from four-membered cyclobutenones accessible from squarate esters using a transition metal-catalyzed skeletal remodeling approach. Key to the success of these transformations is the use of $[Rh(OH)(cod)]_2$ and DEA-Xantphos as the ligands. A relatively wide range of 4-hydroxy-cyclobutenol precursors were easily prepared by Grignard addition to commercially available dialkyl squarate. The overall transformation, which proceeds with acrylonitrile as a coupling partner, is robust, and the conditions tolerate a wide range of functional groups. The functional groups on the oxepane derivatives thus accessed set the stage for diversification. For example, conversion into a 6,7-fused ring or a bridged oxabicycle is readily achieved. Our initially proposed mechanism involves Rh(I)-catalyzed intermolecular and intramolecular conjugate additions to form a fused [3.2.0] bicycle, followed by ring expansion through C–C bond cleavage, and finally conjugate additions to install two alkyl substituents. Several empirical and computational studies partially support the initially proposed Rh(I)-catalyzed reaction pathway. However, calculations also suggest an alternative for the formation of the oxepane-based products through a C–C bond-cleaved Rh(III) intermediate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (NIGMS MIRA R35 GM130345). J.-S.H. is grateful to SK Innovations for a graduate training fellowship. C. N. thanks the NIH for a Ruth L. Kirschstein postdoctoral fellowship. M.-H.B. acknowledges financial support from the Institute for Basic Science in Korea (IBS-R010-A1). We thank Dr. Hasan Celik and UC Berkeley's NMR facility in the College of Chemistry (CoC-NMR) for spectroscopic assistance. Instruments in the CoC-NMR are supported in part by NIH S10OD024998. We thank Dr. Nicholas Settineri (UC Berkeley) and Hyunchul Kwon (UC Berkeley) for assistance with single-crystal X-ray diffraction studies. We also thank Christina Kraml and Dr. Brandon J. Kennedy of Lotus Separations LLC for their assistance with the chiral separation of squaric acid **1u.**

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

REFERENCES

(1). (a)Pereira R; Andrade P; Valentão P. Chemical Diversity and Biological Properties of Secondary Metabolites from Sea Hares of Aplysia Genus. Mar. Drugs 2016, 14, 39. [PubMed: 26907303] (b)Barbero H; Díez-Poza C; Barbero A The Oxepane Motif in Marine Drugs. Mar. Drugs 2017, 15, 361. [PubMed: 29140270] (c)Basu S; Ellinger B; Rizzo S; Deraeve C; Schürmann M.; Preut H.; Arndt H-D.; Waldmann H. BiologyOriented Synthesis of a Natural-Product Inspired Oxepane Collection Yields a Small-Molecule Activator of the Wnt-Pathway. Proc. Natl. Acad. Sci. U.S.A. 2011, 108, 6805–6810. [PubMed: 21415367] (d)Lu Q; Harmalkar DS; Choi Y; Lee K An Overview of Saturated Cyclic Ethers: Biological Profiles and Synthetic Strategies. Molecules 2019, 24, 3778. [PubMed: 31640154] (e)Hoye TR; Kurth MJ Total Synthesis of *dl*-Aplysistatin. J. Am. Chem. Soc. 1979, 101, 5065–5067.(f)Tanaka A; Suzuki M; Yamashita K Total Synthesis of (+)-Palisadin A and (+)-12-Hydroxypalisadin B. Agric. Biol. Chem. 1986, 50, 1069–1071. (g)Funel-Le Bon C; Berrué F; Thomas OP; Reyes F; Amade P Sodwanone, S, a Triterpene from the Marine Sponge *Axinella weltneri*. J. Nat. Prod. 2005, 68, 1284–1287. [PubMed: 16124780] (h)Delost MD; Smith DT; Anderson BJ; Njardarson JT From Oxiranes to Oligomers: Architectures of U.S. FDA Approved Pharmaceuticals Containing Oxygen Heterocycles. J. Med. Chem. 2018, 61, 10996–11020. [PubMed: 30024747]

(2). (a)Sinka V; Martín VS; Cruz DA; Padrón JI Synthesis of Seven Membered Oxacycles: Recent Developments and New Approaches. Eur. J. Org. Chem. 2020, 2020, 6704–6717.(b)Sasaki M; Fuwa H Convergent Strategies for the Total Synthesis of Polycyclic Ether Marine Metabolites. Nat. Prod. Rep. 2008, 25, 401–426. [PubMed: 18389143] (c)Nicolaou KC; Frederick MO; Aversa RJ The Continuing Saga of the Marine Polyether Biotoxins. Angew. Chem., Int. Ed. 2008, 47, 7182–7225.(d)Kleinke AS; Webb D; Jamison TF Recent Progress in the Synthesis of Oxepanes and Medium Ring Ethers. Tetrahedron 2012, 68, 6999–7018.(e)Inoue M Convergent Strategies for Syntheses of *trans*-Fused Polycyclic Ethers. Chem. Rev. 2005, 105, 4379–4405. [PubMed: 16351048] (f)Nakata T Total Synthesis of Marine Polycyclic Ethers. Chem. Rev. 2005, 105, 4314–4347. [PubMed: 16351046] (g)Fujiwara K. Total Synthesis of Medium-Ring Ethers from Laurencia Red Algae. Top. Heterocycl. Chem. 2006, 5, 97–148.

(3). (a)Illuminati G; Mandolini L Ring Closure Reactions of Bifunctional Chain Molecules. Acc. Chem. Res. 1981, 14, 95–102.(b)Casadei MA; Galli C; Mandolini L Ring-closure reactions. 22. Kinetics of cyclization of diethyl (.omega.-bromoalkyl)malonates in the range of 4- to 21-membered rings. Role of ring strain. J. Am. Chem. Soc. 1984, 106, 1051–1056.(c)Galli C; Mandolini L The Role of Ring Strain on the Ease of Ring Closure of Bifunctional Chain Molecules. Eur. J. Org. Chem. 2000, 2000, 3117–3125.

(4). (a)Deiters A; Martin SF Synthesis of Oxygen- and Nitrogen-Containing Heterocycles by Ring-Closing Metathesis. Chem. Rev. 2004, 104, 2199–2238. [PubMed: 15137789] (b)Jiang H; Xu LP; Fang Y; Zhang ZX; Yang Z; Huang Y A Migratory Ether Formation Route to Medium-Sized Sugar Mimetics. Angew. Chem., Int. Ed. 2016, 55, 14340–14344.(c)Rainier JD Synthesis of Natural Products Containing Medium-Size Oxygen Heterocycles by Ring-Closing Alkene Metathesis. In Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts; Cossy J., Arseniyadis S., Meyer C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; Chapter 3, pp 87–127.(d)van den Broek SAMW; Meeuwissen SA; van Delft FL; Rutjes FPJT Natural Products Containing Medium-Sized Nitrogen Heterocycles Synthesized by Ring-Closing Alkene Metathesis. In Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts; Cossy J., Arseniyadis S., Meyer C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; Chapter 2, pp 45–85.

(5). (a)Lakshmipathi P; Grée D; Grée R A Facile C–C Bond Cleavage in the Epoxides and Its Use for the Synthesis of Oxygenated Heterocycles by a Ring Expansion Strategy. Org. Lett. 2002, 4, 451–454. [PubMed: 11820902] (b)Shimizu M; Fujimoto T; Liu X; Hiyama T A Facile Approach to 2-CF_3-Substituted Seven-Membered Oxacycles via Stereoselective Preparation and

Cope Rearrangement of 2-CF_3-*cis*-2,3-Bis(Alkenyl)Oxiranes. Chem. Lett. 2004, 33, 438–439. (c)Cao D; Zhang K; An R; Xu H; Hao S; Yang X; Hou Z; Guo C The Efficient Synthesis of Benzannulated Seven-Membered O-Heterocycles via the Intramolecular Ring-Opening Cyclization of Cyclopropanes. Org. Lett. 2019, 21, 8948–8951. [PubMed: 31674790] (d)French SA; Clark MR; Smith RJ; Brind T; Hawkins BC Expedient Synthesis of Xanthones and Multi-Functionalized Chromones from 1,1-Diacyl Cyclopropanes. Tetrahedron 2018, 74, 5340–5350. (e)Kale BS; Lee H-F; Liu R-S A Sequential Route to Cyclopentenes from 1,6-Enynes and Diazo Ketones through Gold and Rhodium Catalysis. Adv. Synth. Catal. 2017, 359, 402–409.(f)O'Neil KE; Kingree SV; Minbiole KPC A Cyclopropane Fragmentation Approach to Heterocycle Assembly: A Convergent Synthesis of Oxepanes. Org. Lett. 2005, 7, 515–517. [PubMed: 15673278] (g)Ganesh V; Kundu T; Chandrasekaran S σ-Ferrier Rearrangement of Carbohydrate Derived Vinylcyclopropanes: A Facile Approach to Oxepane Analogs. Tetrahedron 2014, 70, 7268–7282.(h)Hewitt RJ; Harvey JE Synthesis of Oxepines and 2-Branched Pyranosides from a d-Glucal-Derived Gem-Dibromo-1,2-Cyclopropanated Sugar. J. Org. Chem. 2010, 75, 955–958. [PubMed: 20067225] (i)Batchelor R; Hoberg JO Diastereoselective Formation of Seven-Membered Oxacycles by Ring-Expansion of Cyclopropanated Galactal. Tetrahedron Lett. 2003, 44, 9043–9045.

(6). Silva SBL; Torre AD; de Carvalho JE; Ruiz ALTG; Silva LF Jr. Seven-Membered Rings through Metal-Free Rearrangement Mediated by Hypervalent Iodine. Molecules 2015, 20, 1475–1494. [PubMed: 25599151]

(7). Nicolaou KC; Yu R; Shi L; Cai Q; Lu M; Heretsch P General Synthetic Approach to Functionalized Dihydrooxepines. Org. Lett. 2013, 15, 1994–1997. [PubMed: 23550898]

(8). Chen P-H; Dong G Cyclobutenones and Benzocyclobutenones: Versatile Synthons in Organic Synthesis. Chem. - Eur. J. 2016, 22, 18290–18315. [PubMed: 27620805]

(9). (a)Birchler AG; Liu F; Liebeskind LS Synthesis of α-Pyridone-Based Azaheteroaromatics by Intramolecular Vinylketene Cyclizations onto the C:N Bond of Nitrogen Heteroaromatics. J. Org. Chem. 1994, 59, 7737–7745.(b)Winters MP; Stranberg M; Moore HW General Enantiospecific Route to Isochromanquinones. Synthesis of (−)-Nanaomycin D. J. Org. Chem. 1994, 59, 7572–7574.(c)Zhang S; Liebeskind LS Cyclobutenedione-Based Method for the Synthesis of Substituted 2-Pyridinones and Dihydro-2-Pyridinones. J. Org. Chem. 1999, 64, 4042–4049. (d)Harrowven DC; Pascoe DD; Guy IL Thermally Induced Cyclobutenone Rearrangements and Domino Reactions. Angew. Chem., Int. Ed. 2007, 46, 425–428.(e)Mohamed M; alves TP.; Whitby RJ.; Sneddon HF.; Harrowven DC. New Insights into Cyclobutenone Rearrangements: A Total Synthesis of the Natural ROS-Generating Anti-Cancer Agent Cribrostatin 6. Chem. - Eur. J. 2011, 17, 13698–13705. [PubMed: 22083951] (f)Harrowven DC; Mohamed M; alves TP.; Whitby RJ.; Bolien D.; Sneddon HF. An Efficient Flow-Photochemical Synthesis of 5H-Furanones Leads to an Understanding of Torquoselectivity in Cyclobutenone Rearrangements. Angew. Chem., Int. Ed. 2012, 51, 4405–4408.(g)Packard E; Pascoe DD; Maddaluno J; Gonçalves TP.; Harrowven DC. Organoytterbium Ate Complexes Extend the Value of Cyclobutenediones as Isoprene Equivalents. Angew. Chem., Int. Ed. 2013, 52, 13076–13079.(h)Harrowven D; Sun W; Wilson D Steric Buttressing Changes Torquospecificity in Thermal Cyclobutenone Rearrangements, Providing New Opportunities for 5H-Furanone Synthesis. Synthesis 2017, 49, 3091–3106.

(10). (a)Li X; Danishefsky SJ Cyclobutenone as a Highly Reactive Dienophile: Expanding Upon Diels–Alder Paradigms. J. Am. Chem. Soc. 2010, 132, 11004–11005. [PubMed: 20698657] (b)Pham HV; Paton RS; Ross AG; Danishefsky SJ; Houk KN Intramolecular Diels-Alder Reactions of Cycloalkenones: Stereoselectivity, Lewis Acid Acceleration, and Halogen Substituent Effects. J. Am. Chem. Soc. 2014, 136, 2397–2403. [PubMed: 24410341]

(11). (a)Kraus JL Reactivity of Organo Lithium Reagents on Dimethyl Squarate: A 1,2-Addition Process Leading to New 2-Hydroxy-3,4 Dimethoxy 3-Cyclobutenone. Tetrahedron Lett. 1985, 26, 1867–1870.(b)Ohno M; Yamamoto Y; Eguchi S Catalysed 1,2-vs. 1,4-Addition of 3,4-Dichlorocyclobut-3-Ene-1,2-Dione with Unsaturated Organosilanes. J. Chem. Soc., Perkin Trans. 1 1991, 2272.(c)Murakami M; Miyamoto Y; Ito Y Stereoselective Synthesis of Isomeric Functionalized 1,3-Dienes from Cyclobutenones. J. Am. Chem. Soc. 2001, 123, 6441–6442. [PubMed: 11427081] (d)Cui M; Oestreich M Synthesis of Silylated Cyclobutanone and

Cyclobutene Derivatives Involving 1,4-Addition of Zinc-Based Silicon Nucleophiles. Chem. -Eur. J. 2021, 27, 16103–16106. [PubMed: 34490934]

(12). (a)Liebeskind LS; Fengl RW 3-Stannylcyclobutenediones as Nucleophilic Cyclobutenedione Equivalents. Synthesis of Substituted Cyclobutenediones and Cyclobutenedione Monoacetals and the Beneficial Effect of Catalytic Copper Iodide on the Stille Reaction. J. Org. Chem. 1990, 55, 5359–5364.(b)Huffman MA; Liebeskind LS Nickel(0)-Catalyzed Synthesis of Substituted Phenols from Cyclobutenones and Alkynes. J. Am. Chem. Soc. 1991, 113, 2771–2772. (c)Kondo T; Nakamura A; Okada T; Suzuki N; Wada K; Mitsudo TA Ruthenium-Catalyzed Reconstructive Synthesis of Cyclopentenones by Unusual Coupling of Cyclobutenediones with Alkenes Involving Carbon - Carbon Bond Cleavage. J. Am. Chem. Soc. 2000, 122, 6319–6320.(d)Yamamoto Y; Kuwabara S; Hayashi H; Nishiyama H Convergent Synthesis of Azabicycloalkenones Using Squaric Acid as Platform. Adv. Synth. Catal. 2006, 348, 2493–2500. (e)Kondo T; Niimi M; Nomura M; Wada K; Mitsudo T Rhodium-Catalyzed Rapid Synthesis of Substituted Phenols from Cyclobutenones and Alkynes or Alkenes via C–C Bond Cleavage. Tetrahedron Lett. 2007, 48, 2837–2839.

(13). (a)Simonot B; Rousseau G Preparation of 3-(n-Alkenoxy)-Propanoic Acids. Synth. Commun. 1993, 23, 549–560.(b)Stewart IC; Bergman RG; Toste FD Phosphine-Catalyzed Hydration and Hydroalkoxylation of Activated Olefins: Use of a Strong Nucleophile to Generate a Strong Base. J. Am. Chem. Soc. 2003, 125, 8696–8697. [PubMed: 12862443] (c)Salah AB; Offenstein C; Zargarian D Hydroamination and Alcoholysis of Acrylonitrile Promoted by the Pincer Complex {κ^{P},κC,κP-2,6-(Ph2PO)2C6H3}Ni(OSO2CF3). Organometallics 2011, 30, 5352–5364. (d)Uesugi S; Li Z; Yazaki R; Ohshima T Chemoselective Catalytic Conjugate Addition of Alcohols over Amines. Angew. Chem., Int. Ed. 2014, 53, 1611–1615.(e)Perdriau S; Zijlstra DS; Heeres HJ; de Vries JG; Otten E A Metal-Ligand Cooperative Pathway for Intermolecular Oxa-Michael Additions to Unsaturated Nitriles. Angew. Chem., Int. Ed. 2015, 54, 4236–4240. (f)Nerush A; Vogt M; Gellrich U; Leitus G; Ben-David Y; Milstein D Template Catalysis by Metal–Ligand Cooperation. C–C Bond Formation via Conjugate Addition of Non-Activated Nitriles under Mild, Base-Free Conditions Catalyzed by a Manganese Pincer Complex. J. Am. Chem. Soc. 2016, 138, 6985–6997. [PubMed: 27164437] (g)Thiyagarajan S; Krishnakumar V; Gunanathan C KOtBu-Catalyzed Michael Addition Reactions Under Mild and Solvent-Free Conditions. Chem. Asian J. 2020, 15, 518–523. [PubMed: 31957937]

(14). Other Michael acceptors, including acrylate derivatives, α,β-unsaturated ketones, and dicyanoalkenes, did not exhibit any reactivity or led to complex mixtures.

(15). Ham JS; Park B; Son M; Roque JB; Jurczyk J; Yeung CS; Baik MH; Sarpong R C–H/C–C Functionalization Approach to N-Fused Heterocycles from Saturated Azacycles. J. Am. Chem. Soc. 2020, 142, 13041–13050. [PubMed: 32627545]

(16). (a)Shen Z; Khan HA; Dong VM Rh-Catalyzed Carbonyl Hydroacylation: An Enantioselective Approach to Lactones. J. Am. Chem. Soc. 2008, 130, 2916–2917. [PubMed: 18278919] (b)Phan DHT; Kim B; Dong VM Phthalides by Rhodium-Catalyzed Ketone Hydroacylation. J. Am. Chem. Soc. 2009, 131, 15608–15609. [PubMed: 19813746]

(17). The Jaguar program package was used for the calculations. The B3LYP-D3 level of theory was used with the 6–31G**/LAVCP basis set for geometry optimization, frequencies, and solvation calculations. Single-point energies were reevaluated with the cc-pVTZ(-f)/LACV3P basis set. More details are given in the Supporting Information.

(18). Masuda Y; Hasegawa M; Yamashita M; Nozaki K; Ishida N; Murakami M Oxidative Addition of a Strained C–C Bond onto Electron-Rich Rhodium(I) at Room Temperature. J. Am. Chem. Soc. 2013, 135, 7142–7145. [PubMed: 23641905]

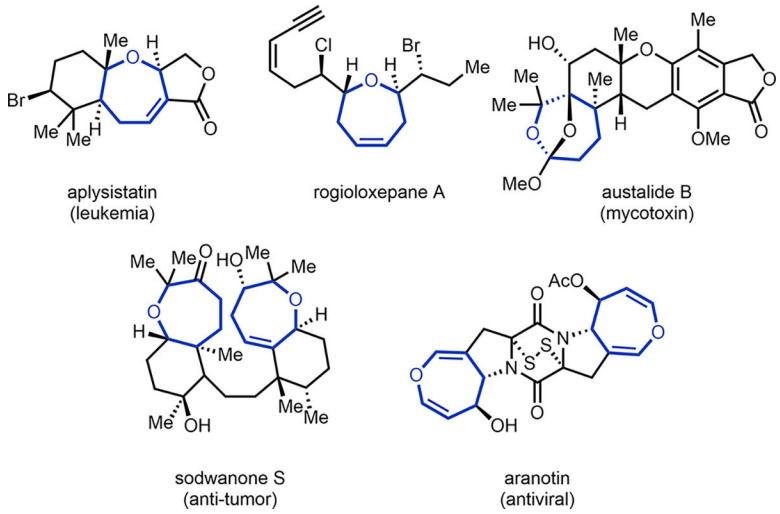


Figure 1.
Selected examples of bioactive natural products featuring derivatized oxepane scaffolds.

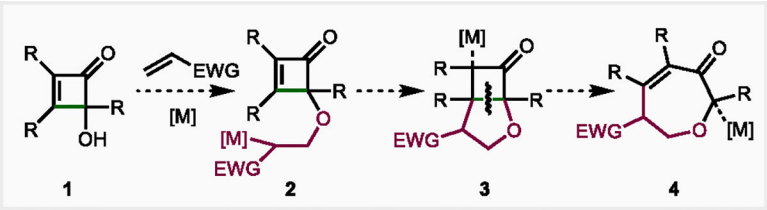


Figure 2.
Proposed cascade conjugate addition/C–C bond cleavage approach to oxepane derivatives.

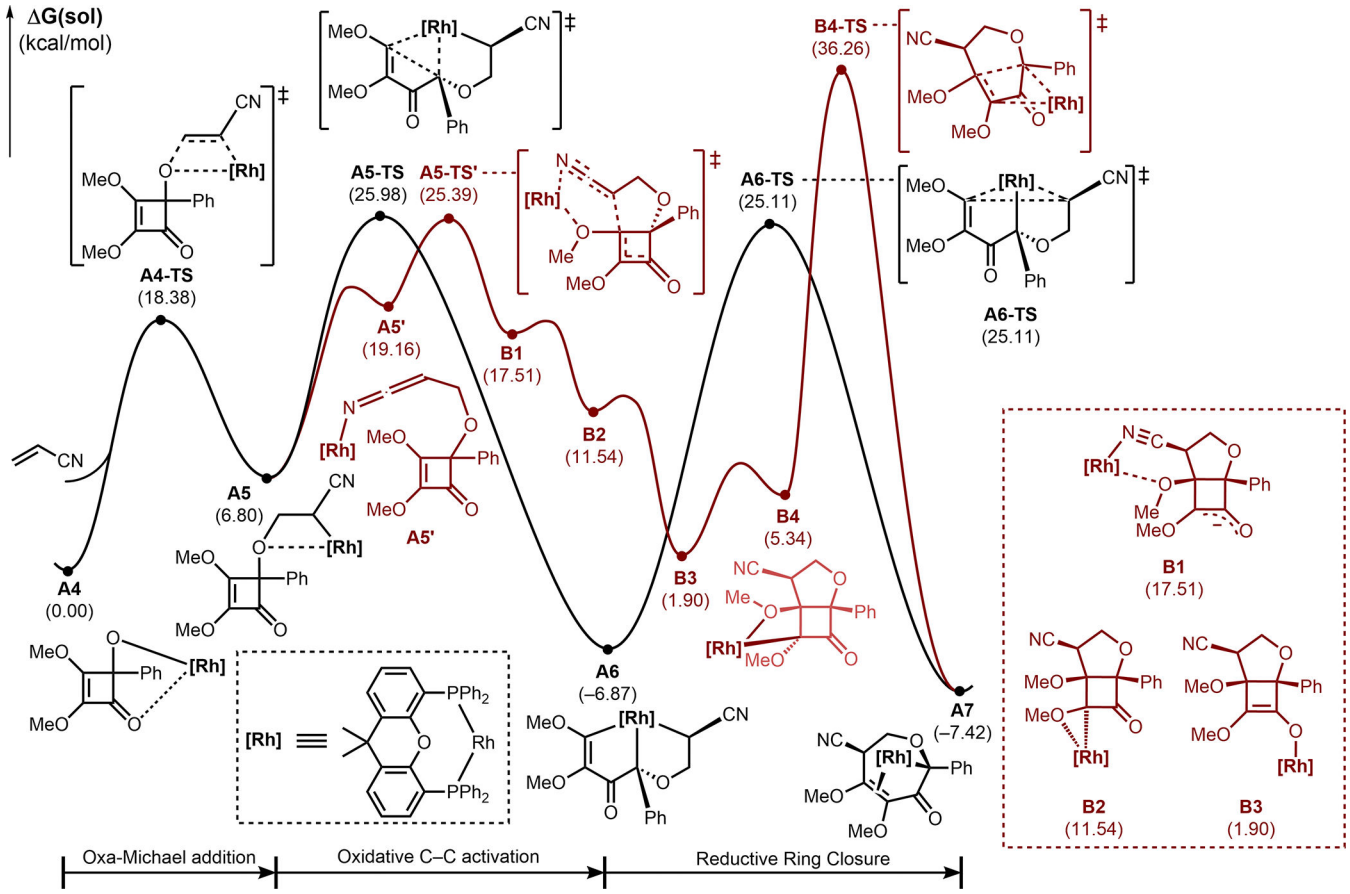
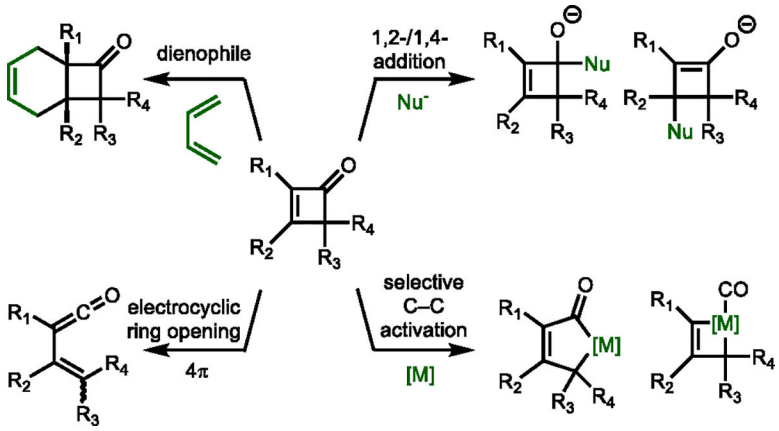
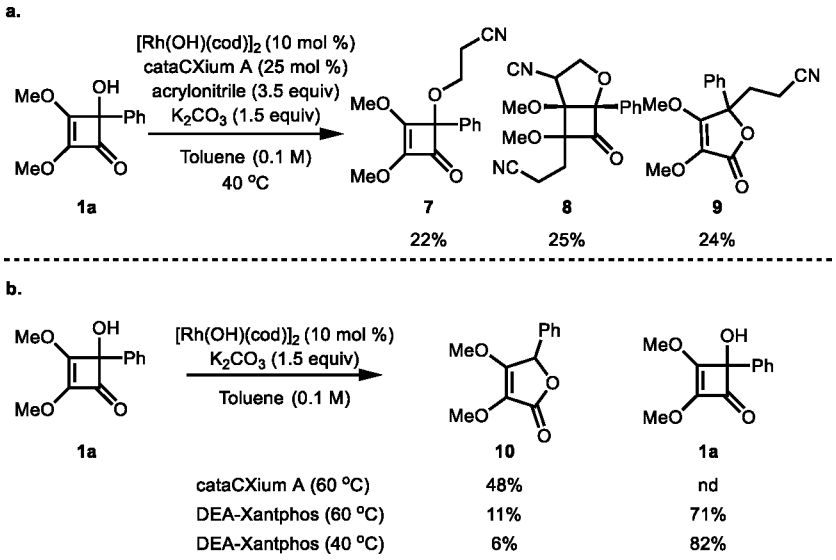


Figure 3.
Free energy profile of the proposed mechanism.



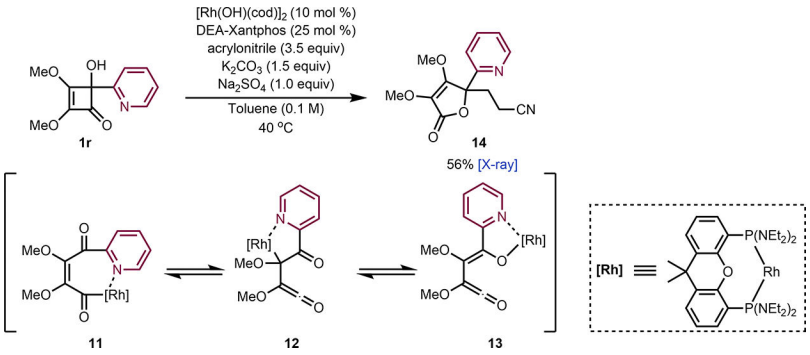
Scheme 1.

Some Established Transformations of the Squaric Acid-Derived Cyclobutenone Scaffold

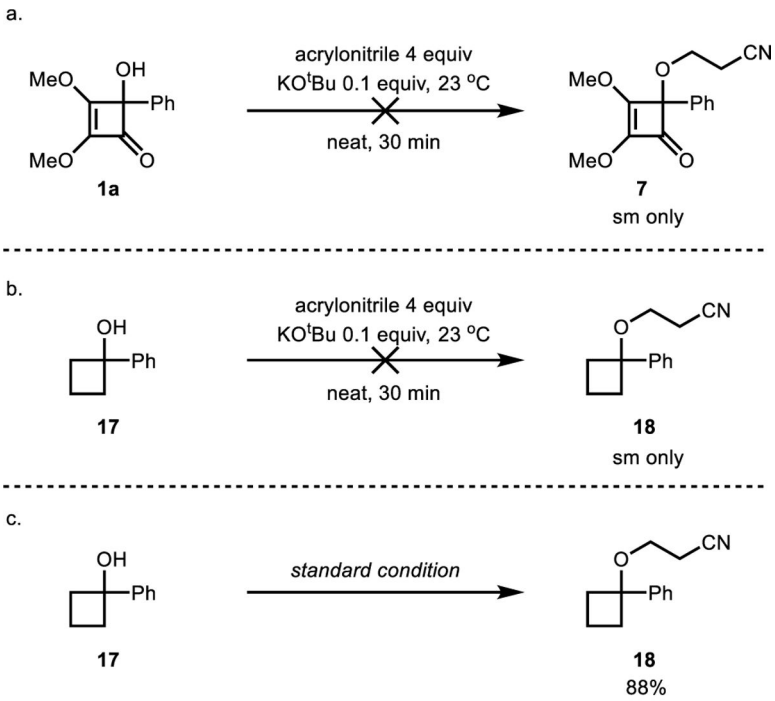


Scheme 2.

(a) Different Rearrangement Outcomes Observed Using cataCXium A; (b) Rearrangement of 1a Using Rh Precatalyst and cataCXium A or DEA-Xantphos as Ligands without the Electrophile

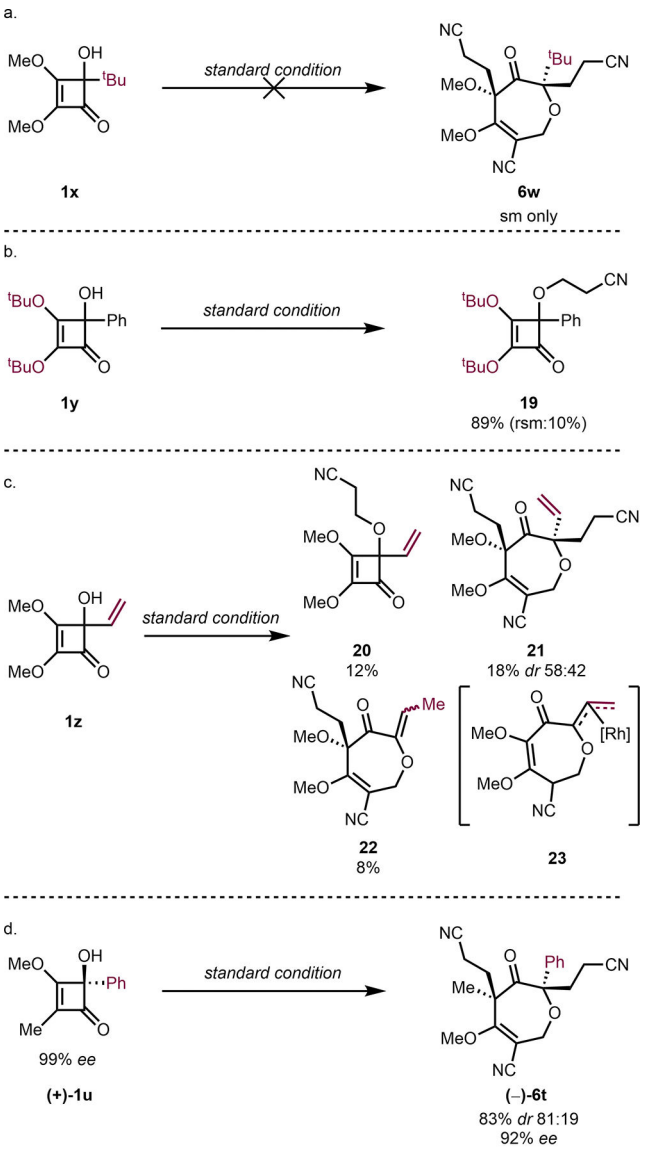


Scheme 3.
Rearrangement of 2-Substituted Pyridine



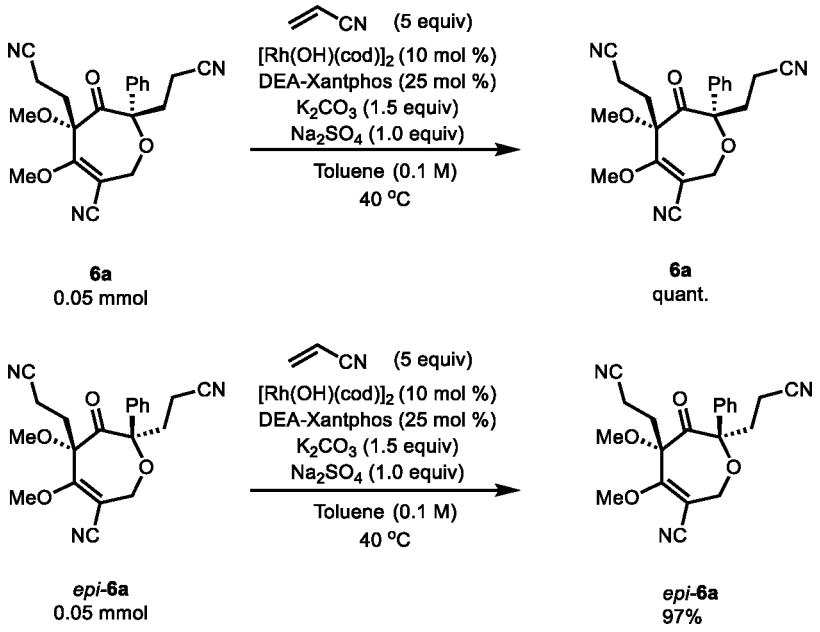
Scheme 4.

Probing Oxa-Michael Addition: (a, b) No Oxa-Michael Products (7 or 18) Were Observed under Basic Condition without the [Rh(OH)(cod)]$_2$ Catalyst; (c) Formation of the Oxa-Michael Product in the Presence of [Rh(OH)(cod)]$_2$

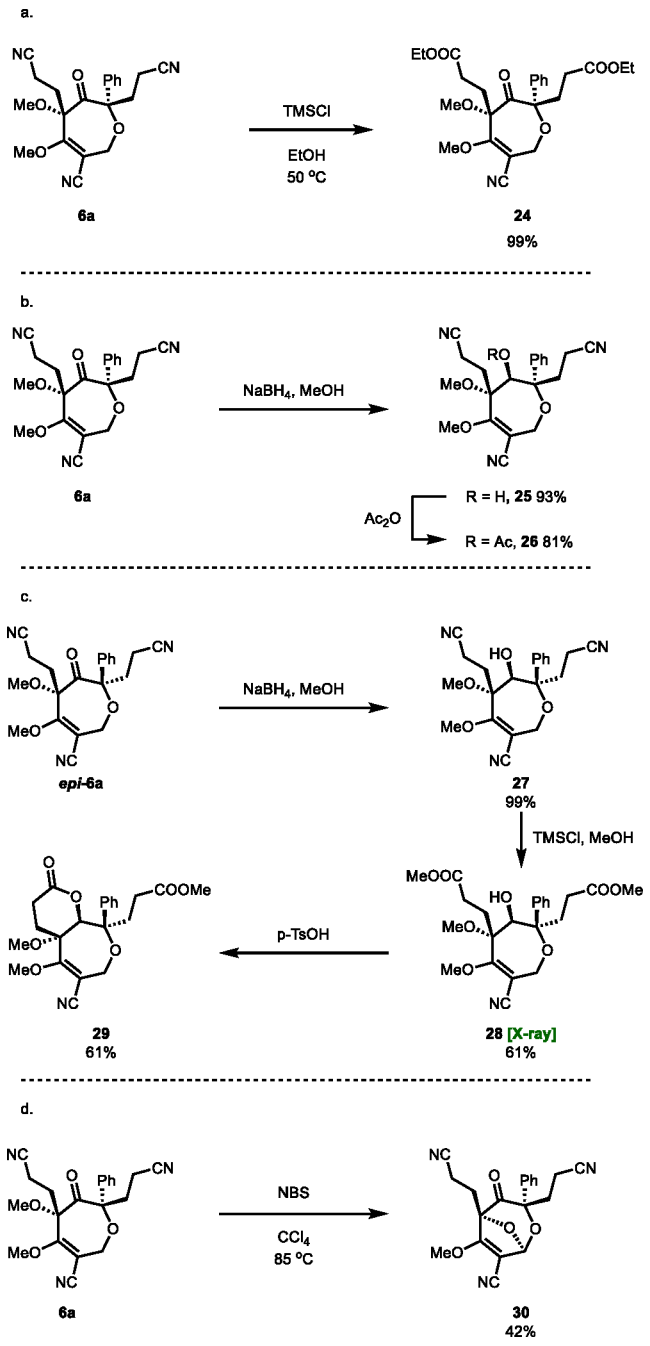


Scheme 5.

Probing the Efficiency of Oxacycle Formation: (a) Steric Environment in Tertiary Alcohol; (b) Steric Environment in Alkene Substituents; (c) Isomerization of the Ring Expansion Intermediate; (d) Stereospecific Product Formation



Scheme 6.
Lack of Interconversion of Observed Diastereomers

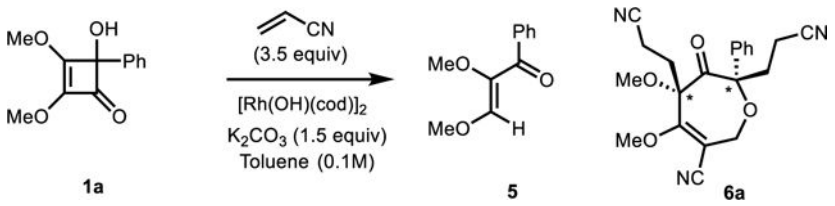


Scheme 7.

Derivatizations of the Oxepane Scaffold: (a) Pinner Reaction to Convert Primary Cyano Groups into Esters; (b) Stereoselective Reduction of a Carbonyl Group; (c) Formation of a Fused Bicycle Structure through Multistep Manipulation of Existing Functional Groups; (d) [3.2.1] Bridged Ring Formation

Table 1.

Preliminary Study of 6a Formation from Cyclobutenol 1a[a]



entry	[Rh] (mol %)	Xantphos (mol %)	time (h)	temp (°C)	yields[b,c]
1	10	25	1	100	**5** 37%, **6a** 23%, *dr* 63:37
2	10	25	1	80	**5** 24%, **6a** 41%, *dr* 59:41
3	10	25	20	40	**6a** 61%, *dr* 65:35
4	10	25	20	23	**1a** 9%, **6a** 51%, *dr* 65:35
5	–	25	20	40	**1a** 80%
6	10	–	20	40	**1a** 84%
7[d]	10	25	20	40	**6a** 56%, *dr* 68:32
8	–	–	20	40	**1a** 99%
9[e]	10	25	20	40	**1a** 45%, **6a** 12%, *dr* 59:41
10[f]	10	25	20	40	**1a** 6%, **6a** 50%, *dr* 66:34

[a] The reaction was performed with cyclobutenol **1a** (0.10 mmol).

[b] ^{1}H NMR conversion of **11a** using trimethoxybenzene as the internal standard.

[c] *dr* was determined by the ^{1}H NMR integration of resonances corresponding to diastereomers in the crude NMR mixture.

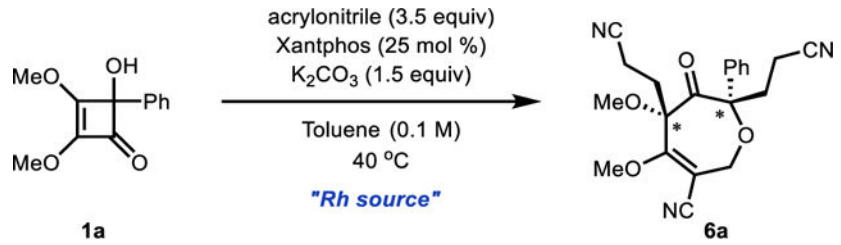
[d] In the absence of K_2CO_3.

[e] Dioxane was used as the solvent.

[f] 0.2 M in toluene.

Table 2.

Catalyst Screening for 6a Formation[a]



entry	catalyst	yields[b,c]
1	$[Rh(cod)OH]_2$	**6a** 61%, *dr*65:35
2	$[Rh(cod)OMe]_2$	**6a** 40%, *dr* 69:31
3	$[Rh(cod)CI]_2$	**1a** 88%
4	$Rh(C_2H_2)_2(acac)$	**1a** 88%
5	$Rh(cod)(MeCN)_2BF_4$	**1a** 87%
6	$Rh_2(OAc)_4$	**1a** 95%
7	$Rh_2(TFA)_4$	**1a** >99%
8	$Cp^*(MeCN)_3Rh(SbF_6)_2$	**1a** >99%

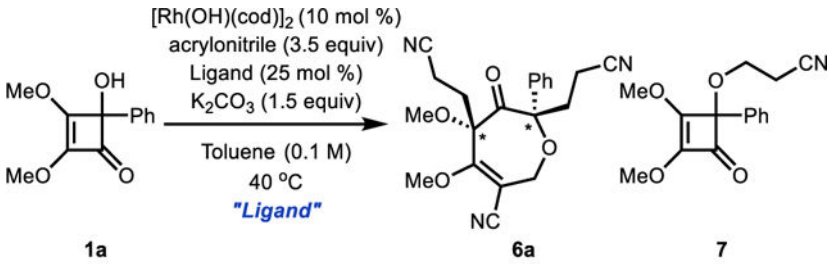
[a]The reaction was performed with cyclobutenol **1a** (0.10 mmol) and Rh catalyst, 10 mol %.

[b]^{1}H NMR conversion of **11a** using trimethoxybenzene as the internal standard.

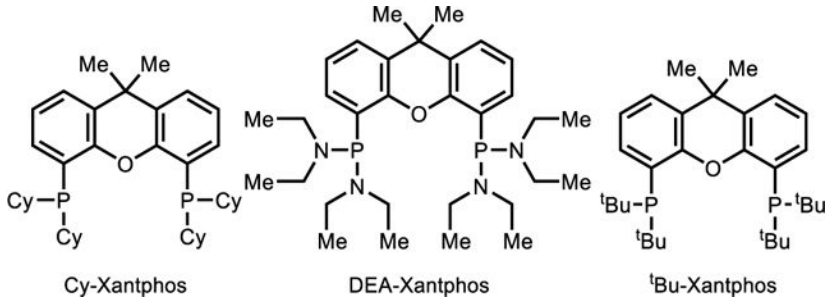
[c]*dr* was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude NMR mixture.

Table 3.

Ligand Effects on 6a Formation[a]



entry	ligand	yield[b]
1	Xantphos	**6a** 61%, dr 65:35
2	PPh_3	**6a** 37%, *dr* 58:42
3	rac-BINAP	**1a** 74%
4	Davephos	**1a** 24%
5	RuPhos	**1a** 46%
6	XPhos	**1a** 87%
7	(S)-DTBM-SEGPHOS	**6a** 20% *dr* 48:52, **1a** 28%
8	Cy-Xantphos	**6a** 66%, *dr* 62:38
9	DEA-Xantphos	**6a** 72%, *dr* 58:42
10[c]	DEA-Xantphos	**6a** 81%, *dr* 54:46
11	^{t}Bu-Xantphos	**1a** 31%, 7 40%



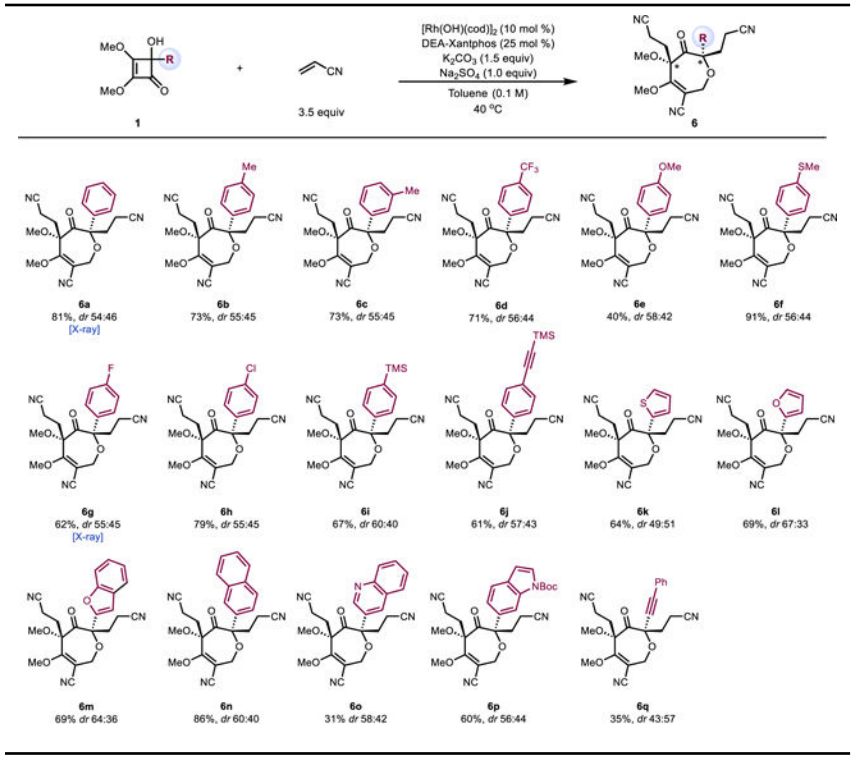
[a]The reaction was performed with cyclobutenol **1a** (0.10 mmol).

[b]^{1}H NMR yield using trimethoxybenzene as the internal standard. *dr* was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude NMR mixture.

[c]1.0 equiv of anhydrous Na_2SO_4 was added.

Table 4.

Scope of Oxacycle Formation Using 1 as the Starting Material



J Org Chem. Author manuscript; available in PMC 2024 December 15.

Table 5.

Variations of the C1 and C2 Substituents