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ARTICLE

Metal-free [3+2] cycloadditions of alkylidene cyclopropanes via a non-classical "bow-tie" cation

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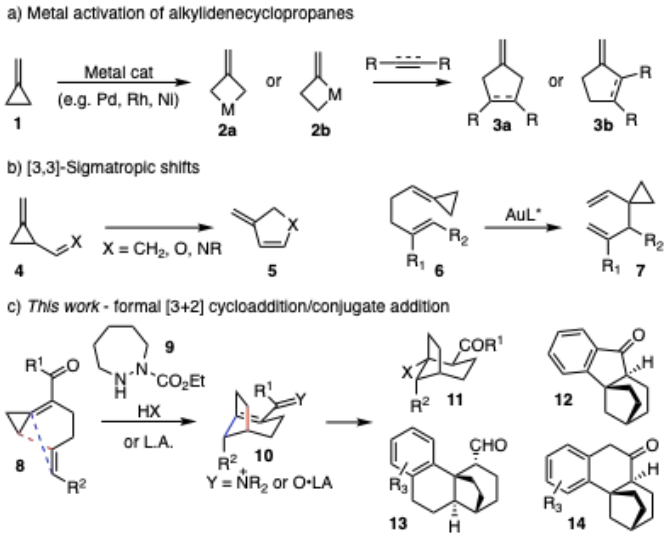
Abstract: Treatment of cyclopropylidene-containing 1,5-hexadienes with either diazepane carboxylate organocatalysts or Lewis acids initiates a tandem Michael addition – cyclopropane ring-opening (MACRO) sequence resulting in the formation of [3.2.1]-bridged bicycles. DFT calculations suggest the reaction proceeds through a non-classical corner-alkylated cyclopropane which facilitates an uncommon 1,3-ring expansion of the cyclopropane. The rearrangement generates a reactive bridgehead enone/eniminium which can be trapped intermolecularly by HCl or intramolecularly by electron-rich arenes to generate bridged tetracycles. The method has the potential to furnish functionalized polycycles applicable to natural product synthesis.

Introduction

Alkylidenecyclopropanes (ACPs) are versatile units in organic chemistry. The combination of ring strain merged with alkene functionality permits a wide variety of reactivity modes which can be utilized in complex molecule synthesis.[1] Perhaps best known are metal-catalyzed reactions which insert into either the proximal or distal bond to generate metallocycle intermediates (Scheme 1a).[2-5] These metallocycles include trimethylenemethanes (TMM, **2a**), which can be used in a variety of cycloadditions, with intramolecular examples usually furnishing fused bicyclic products. ACPs have also been used in the context of sigmatropic rearrangements (Scheme 1b). These include examples where the ACP is fully integrated into the reaction and the cyclopropane undergoes fragmentation to generate methylene cyclopentanes[6], as well as examples where the cyclopropane is a more passive component, exerting only a thermodynamic driving force ($sp^2 \rightarrow sp^3$ strain release) to Cope rearrangements.[7] Cyclopropanes are also well-established for their ability to ring-expand under cationic conditions, with the predominant mode being 1,2-shifts in cyclopropylcarbinyl cations to form cyclobutyl products.[8-11] Examples of larger expansions of cyclopropanes remain very limited.[12-15] Solvolytic 1,3-ring expansions of cyclopropylethyl systems to cyclopentanes have been noted in only a few cases, and are usually accompanied by significant chemo- and regioselectivity issues.[16-18]

In the context of studying organocatalytic Cope-rearrangements catalyzed by cyclic hydrazides[19-21], we identified a novel reactivity pattern of ACPs which features an alkene conjugate addition followed by 1,3-cyclopropane expansion onto an incipient cation (Scheme 1c). The net result is a metal-free [3+2] cycloaddition that furnishes bridged bicyclic products, in contrast to fused bicyclic products usually formed from metal TMM complexes. Moreover, the mechanism of this reaction is sufficiently robust that it is not limited to organocatalytic initiation, as Lewis and Brønsted acid activation can unlock similar reactivity depending on the substrate. Moreover, this chemistry generates a highly reactive bridgehead cation and/or anti-Bredt bridgehead enone/eniminium ion which can be trapped by halides or internal nucleophiles to generate a diverse array of structurally complex systems.



Scheme 1: a) Overview of conventional metal catalyzed modes of ring opening for ACPs b) ACP containing sigmatropic shifts c) Transition metal-free ring-opening of ACPs in diverse substrate classes.

Results and Discussion

The initial discovery of the reaction was with alkylidenecyclopropane **15a**, prepared by a modified HWE reaction between a substituted homoallyl-phosphonate and *in situ* generated cyclopropanone (see Supporting Info for details)[22]. Thermolysis of **15a** in toluene at 120 °C for 20 h proceeded to afford the expected Cope-rearrangement product **16a** in 73% yield (Scheme 2). Reaction of substrate **15a** under organocatalytic conditions using **9•HCl** (20 mol%) in acetonitrile at room temperature, the reaction stalled after low conversion to product. Increasing to a stoichiometric amount of **9•HCl** (1.2

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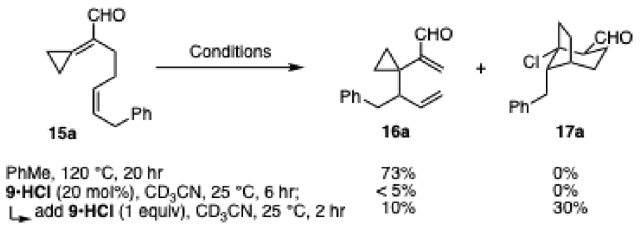
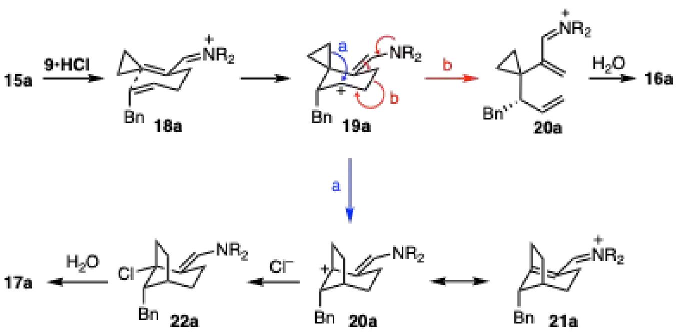
equiv), resulted in complete consumption of the starting material within 2 h. While a small amount of the Cope product **16a** was still observed, the major product lacked not only alkene protons, but also any evidence of a cyclopropane. Analysis by 1D and 2D NMR along with HRMS revealed that the product was [3.2.1]-bridged bicycle **17a**.



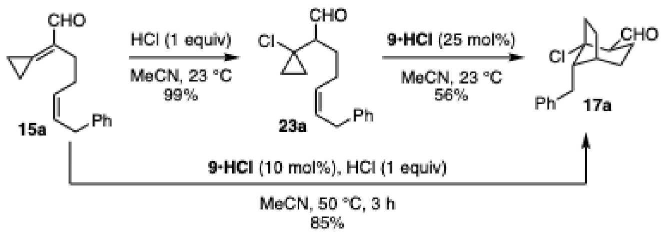
Scheme 2: Novel ring expansion of cyclopropylidene-containing 1,5-hexadienes.

Bridged bicycle **17a** is formally a [3+2] addition product of the terminal alkene across the cyclopropane accompanied by conjugate addition of HCl to the enal. It is notable that this is accomplished without the need for metal catalysis and provides **17a** as a single diastereoisomer. A postulated route to **17a** was informed by prior investigations into hydrazide-catalyzed Cope rearrangements that showed that the reaction could be initiated by addition of an alkene onto an α,β-unsaturated iminium ion to form an intermediate cation[23] (e.g. **18a**→**19a**, Scheme 3) that then fragments by retro-conjugate addition (path b) to afford formal Cope products **20a/16a** in a stepwise fashion.[19-20] In the case of the path towards **17a**, we postulated that the cyclopropane expands via an uncommon 1,3-shift (path a) to afford bridgehead cation **20a**, which could potentially be stabilized by the adjacent enamine as the anti-Bredt α,β-unsaturated eniminium **21a**. Intermediate **20a/21a** is then trapped by chloride prior to hydrolysis of the catalyst. The consumption of HCl in the formation of **17a** was presumably responsible for the reaction stalling when catalytic amounts of **9•HCl** were employed, as the reaction is depleted of acid co-catalyst.



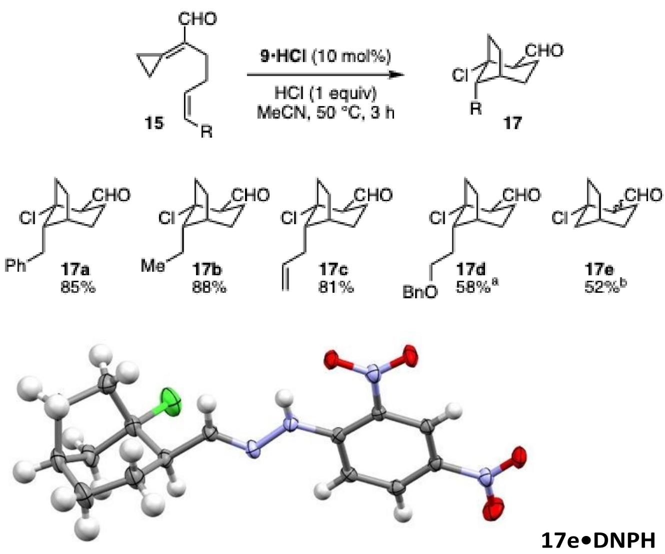
Scheme 3: Postulated mechanism for bicycle formation.

With the potential of this *Michael addition – cyclopropane ring-opening* (MACRO) reaction for bridged bicycle synthesis, we optimized the reaction conditions, first by examining the amount of HCl employed. Treatment of **15a** with one equivalent of HCl in the absence of **9** rapidly afforded **23a** in nearly quantitative yield resulting from simple conjugate addition of HCl to the strained enal (Scheme 4).[24-25] Subsequent treatment of **23a** with 25 mol% of **9•HCl** transformed chloride **23a** to **17a** in 56% yield, presumably by regenerating the eniminium *in situ*. Combining the two-step process in a single pot reaction using 1 eq. of HCl with 10 mol% of **9•HCl**, and increasing the temperature to 50 °C afforded **17a** in an acceptable 85% yield. A solvent screen revealed that our initial choice, MeCN, was optimal (see Supporting Info). We screened additional acids to see if trapping with other external nucleophiles was feasible, but observed only β-addition with weaker acids ($PhSO_2H$, HN_3, AcOH) and decomposition with acids such as HBr, TFA and TfOH.



Scheme 4: MACRO reaction optimization.

With an optimized set of conditions in hand, we examined a range of different substrates. Ethyl and allyl substituents on the alkene rearranged in good to excellent yields, and a terminal benzyloxy group was also well tolerated (Scheme 5). In all cases, the relative stereochemistry of the product was identical to that observed in **17a,** with the alkene substituent axial on the six-membered ring. Additionally, a simple vinyl substrate was also found to react efficiently, affording **17e** in 52% yield, though the reaction was slower in this case, requiring 48 h to reach completion. Fortuitously, the dinitrophenyl hydrazone of **17e** was crystalline, allowing for confirmation of the identity of the ring-expanded products. We did note a few limitations of the reaction – methyl substitution at the 5-position of the 1,5-hexadiene prevented the ring-expansion reaction. This was presumably due to increased stability of the intermediate cation, inhibiting the postulated 1,3-shift, affording only Cope-rearrangement product. Additionally, conjugated substituents on the alkene (e.g. phenyl, vinyl, ethynyl) were all incompatible, giving mixtures of Cope and decomposition products.



Scheme 5: Scope of *cis*-alkene substrates in the MACRO reaction and the x-ray structure of **17e** as the corresponding 2,4-dinitrophenylhydrazone. a) Reaction employed 20 mol% **9•HCl** for 16 h. b) Reaction time = 48 h. Product isolated as a 2:1 mixture of equatorial/axial mixture

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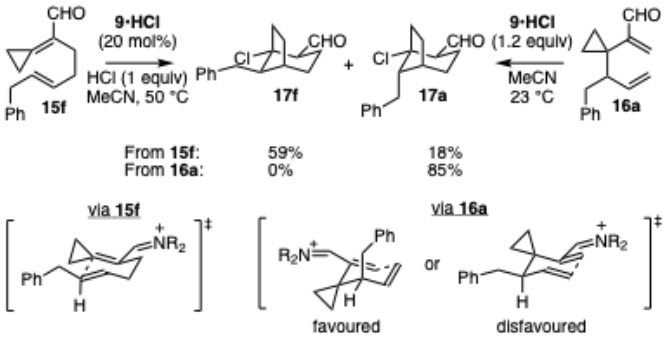
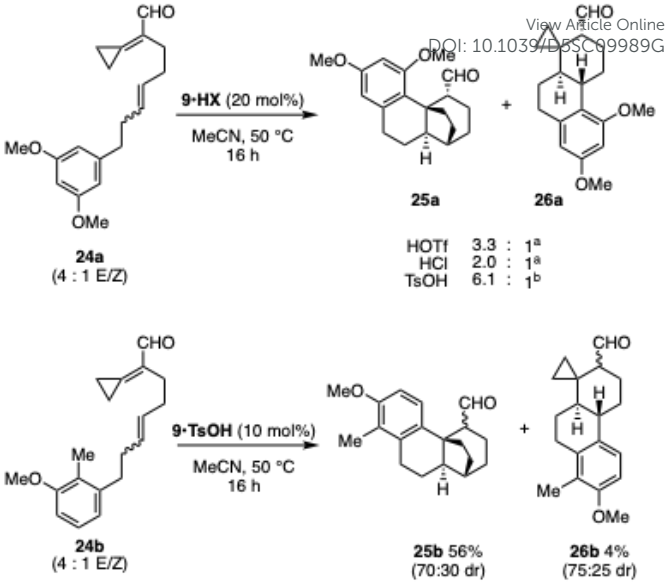
To diversify the stereochemistry of the products, a *trans*-alkene substrate was investigated. Treatment of **15f** under the standard conditions indeed generated equatorial product **17f** in an acceptable 59% yield (Scheme 6). Intriguingly, the product was accompanied by 18% of the corresponding axial isomer **17a**. This was initially unexpected as the mechanism in Scheme 4 suggests that the stereochemistry should be set via a six-membered ring transition state. The most likely source of epimer **17a** is via the Cope-rearrangement product **16a**, which our initial experiments demonstrated is a viable intermediate. This was supported by treatment of **16a** under our standard conditions, which generated **17a** exclusively. Although chair-like transition states typically favour equatorial disposition of alkyl groups, the cyclopropane imparts an unusual steric and stereoelectronic influence which strongly favours the benzyl group in an axial position.[26]



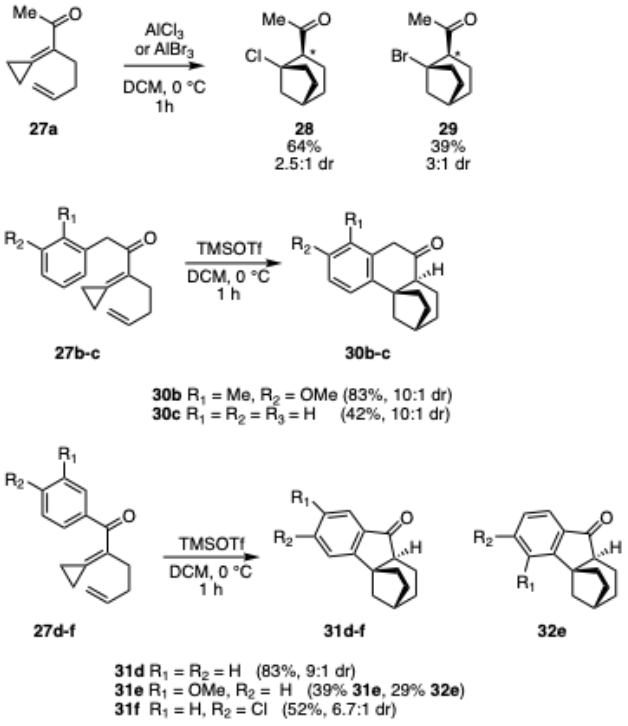
Scheme 6: MACRO reaction of a *trans*-alkene substrate.

It was possible to take advantage of the postulated bridgehead cation/eniminium (e.g. **20a/21a**) to access more complex architectures by trapping with internal nucleophiles. As an example, polyene cyclization of **24a** bearing an electron-rich arene successfully generated the desired tetracycle **25a**, accompanied by lesser amounts of direct polyene product **26a** resulting from trapping of the cation prior to ring expansion in an overall yield of 71% (Scheme 7).[27] In contrast to the halocyclization, arene trapping did not require addition of stoichiometric acid and could be achieved with catalytic amounts of **9** and acid co-catalyst. In the case of HCl as co-catalyst, both **25a** and **26a** were isolated as inseparable mixtures of diastereomers at the α-aldehyde position. The reaction could be conducted with several co-catalysts, with TsOH affording the best yield and ratio of rearranged to direct polyene product as well as providing single diastereomers of both **25**a and **26a**. These conditions could be equally applied to substrate **24b**, affording a 56% yield of the desired bridged tetracycle using only 10 mol% of catalyst **9**. In both **25a** and **25b**, we noted that the axial aldehyde epimer was favoured, presumably due to eclipsing interactions with the arenes.



Scheme 7: Intramolecular trapping to form bridged tetracycles. a) Inseparable mixture of isomers. b) Isolated yield of **25a** = 61%.

The MACRO reaction process can be generalized to other methods of initiating the conjugate addition. For instance, ketone substrates, while resistant to organocatalytic activation (due to sterics) could be induced to cyclize by Lewis acids.[28] Treatment of **27a** with 1 equiv. of $AlCl_3$ afforded chloride trapping product **28** in 64% yield as a 2.5:1 mixture of diastereomers at the α-carbon (Scheme 8). Although we had not been able to trap with other halides in the organocatalytic reactions of **15**, the use of $AlBr_3$ was successful at affording **29** in 39% yield, again as a mixture of diastereomers (3 : 1 eq : ax).



Scheme 8: Lewis acid catalyzed MACRO reactions of ketones.

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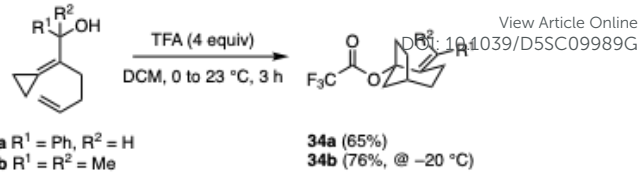
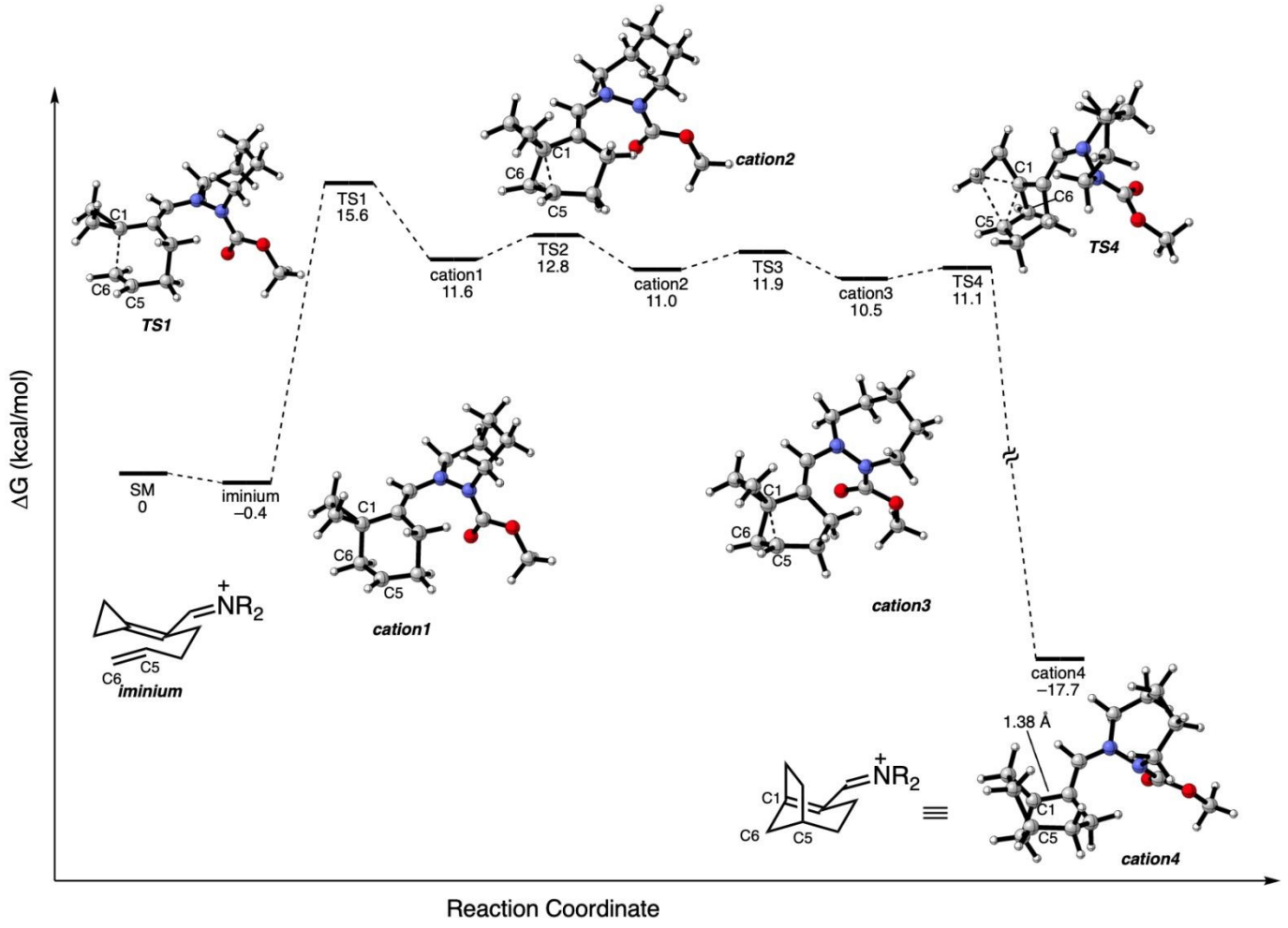
We then examined substrates containing internal nucleophiles. Treatment of electron rich benzylic ketone **27b** with TMSOTf gave the intramolecular cyclization product **30b** in 83% yield, with a *dr* of 10 : 1. The reaction could also be conducted with less nucleophilic arene **27c**, albeit in a slightly reduced yield (42%, 10:1 *dr*). In addition to benzyl groups as intramolecular traps, simple phenyl groups could also be induced to cyclize. Treatment of **27d** with TMSOTf cleanly afforded the cyclized product **31d** in 83% yield (9:1 *dr*). Similarly, reaction with 3-methoxybenzoyl substrate **27e** afforded intramolecular trapping in 68% overall yield as a 57:43 ratio of 1,2,4- and 1,2,3-trisubstituted regioisomers (**31e** and **32e**). Finally, reaction of 4-chlorobenzoyl substrate **27f** afforded cyclization product **31f** in a slightly lower yield of 52%, (*dr* = 6.7 : 1), presumably due to the reduced nucleophilicity of the arene.

Finally, initiation of the MACRO process is not limited to α,β-unsaturated carbonyls. Treatment of allylic alcohols such as **33a/b** with TFA (4 eq.) in DCM (Scheme 9) afforded efficient cyclizations, presumably via allyl cation intermediates.[29] In both cases, the presumed bridgehead cation was trapped by trifluoroacetate, affording **34a** and **34b** in 65% and 76% yield respectively.[30]



Scheme 10: MACRO reaction initiated by ionization of allylic alcohols.

While 1,2-cation-initiated expansions of cyclopropanes to cyclobutane[8, 31-32] products are common, often occurring via non-classical bicyclobutonium ions,[11, 33] examples of 1,3-shifts are quite limited.[12, 34-35] We thus examined the reaction by DFT to shed light on this unusual rearrangement. Calculations at the M06-2X/6-311+G(d)[36] level using PCM solvation[37-39] for acetonitrile were conducted using unsubstituted substrate **16e** and identified several transition states for conjugate addition of the terminal alkene (at C6) to the α,β-unsaturated iminium ion (at C1). As in prior studies on Cope rearrangement and polyene cyclizations, the most stable transition state (***TS1,*** 15.9 kcal/mol relative to the starting iminium) was chair-like with the carbamate positioned over the ring (Scheme 10).[19-20, 23, 40-41] An IRC calculation[42] connected the transition state with ***cation1*** (+11.7 kcal/mol relative to the iminium) which is a localized 2° cation equivalent to structure **19a**. This intermediate had two



Scheme 9: Reaction coordinate diagram for MACRO reaction. DFT results at the M06-2X/6-311+G(d) (PCM=acetonitrile) level of theory.

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pathways available to it. The first was a low barrier (1.4 kcal/mol) pathway leading to Cope product **16a** (see Supporting Information). Alternatively, a similarly low barrier ***TS2*** (1.2 kcal/mol) led to non-classical ***cation2*** (Scheme 10 and Figure 1).

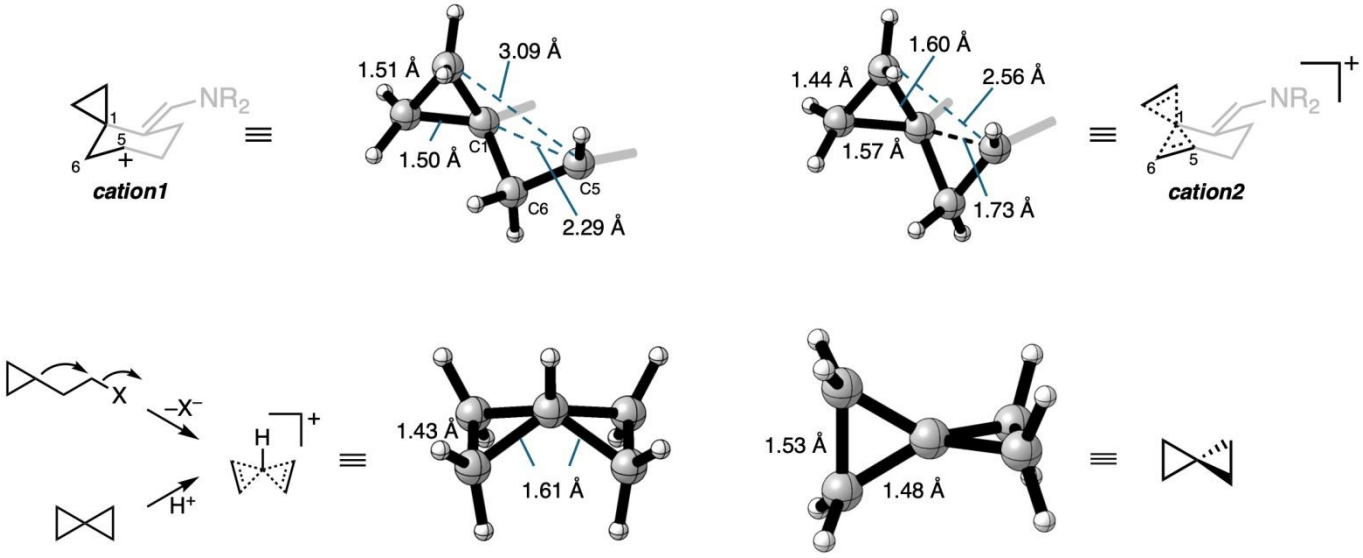


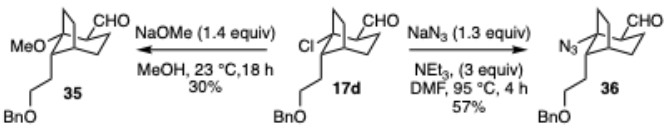
Figure 1: Close-up views of classical ***cation1***, non-classical ***cation2***, as well as a minimal non-classical cation and comparison to spiro[2.2]pentane. All calculations at the M06-2X/6-311+G(d) (PCM=acetonitrile) level of theory.

In ***cation2***, C1 bridges between both C6 and C5 of the cation, with a bond length of 1.73 Å from the C1 to C5 (Figure 1), compared to a distance of 2.29 Å between the same atoms in classical ***cation1***. Notably, there are also changes in bond lengths in the cyclopropane (lengthening of the bonds to the central carbon and shortening of the distal bond) consistent with the hypercoordinate nature of C1. ***Cation2*** is effectively a corner-alkylated cyclopropane which is also spiro-fused to a second cyclopropane. Such intermediates have been suggested in assisting solvolysis in cyclopropanes fused to bridged bicycles.[13, 18, 43-44] We modeled a simplified system (Figure 1) that would result from ionization of a (2-haloethyl)cyclopropane or center protonation of spiro[2.2]pentane (Figure 1). In the model, which is not constricted by fusion into an additional ring, the cation is C_{2v} symmetric possessing lengthened cyclopropane bonds to the central atom and shortened distal C-C bonds bearing partial π-character, as compared to spiro[2.2]pentane. Given its physical resemblance, we have nicknamed this species a "bow-tie" cation.[45] Importantly, the changes in geometry moving from classical ***cation1*** to non-classical bow-tie ***cation2*** bring the two atoms involved in the 1,3-shift, the pseudoaxial methylene of the cyclopropane and C5, closer together (from 3.09 Å to 2.56 Å). A ring flip from a half-chair to a twist-boat conformation (via ***TS3***, Scheme 10) shortens this distance further to 2.49 Å in ***cation3*** and subsequent ring-expansion/1,3-shift takes place via ***TS4*** with a very shallow barrier (0.6 kcal/mol).[46] Notably, a direct cyclopropane expansion path from ***cation1*** to a bridgehead cation/eniminium could not be located, suggesting that the evolution to the non-classical cation is necessary in this case to promote the 1,3-shift. Additionally, while adding alkyl substituents to the terminus of the 1,6-diene did not affect the calculations significantly, including a phenyl group on the terminal alkene resulted in a shift from the non-classical cation to a 5-membered ring bearing an exocyclic benzylic cation, suggesting that the failure of conjugated substrates was electronic rather than steric in nature.

Cation4, resulting from the cyclopropane expansion, can formally be thought of as equivalent to bridgehead cation **20a**.

However, as we postulated, ***cation4*** is stabilized significantly by the adjacent enamine as evidenced by a bond length of 1.38 Å, consistent with significant bridgehead double bond character (e.g. **21a**).[47] While this would formally be an anti-Bredt olefin[48], bridgehead alkenes in [3.2.1]-bicycles have ample precedent.[49-53] The parent anti-Bredt [3.2.1]-olefin has been predicted to have a strain energy of 28.6 kcal/mol[49], and offers a plausible explanation for the facile cyclizations of substrates **27d-f**. While these arenes are less nucleophilic, their closures may proceed via a Nazarov-like mechanism rather than a traditional electrophilic aromatic substitution, as is likely with **24a/b** and **27b/c**.

Finally, the Michael addition/cyclopropane expansion process produces complex bridged polycyclic structures with the ability to incorporate groups at numerous positions. In addition, the cyclization leaves several handles for subsequent functionalization. Notably, beyond the obvious potential modifications of the carbonyl functionality, the intermediacy of a bridgehead olefin suggested the possibility of nucleophilic substitution of the halide. To this end, treatment of **17d** with sodium methoxide regenerates the bridgehead olefin *in situ,* which is then trapped as the corresponding methyl ether **35** (Scheme 11). In addition, it was also possible to regenerate the bridgehead enal using triethylamine at elevated temperatures, which allowed trapping with sodium azide to form **36** in 57% yield.



Scheme 11: Derivatization of bridgehead halides by elimination/addition.

Conclusion

We have identified a novel Michael addition – cyclopropane ring-opening (MACRO) sequence that taps into new reactivity of alkylidenecyclopropanes. The reaction may be initiated by a diazepane carboxylate organocatalyst, in the case of aldehyde substrates, while reactions of ketone and allylic alcohol substrates are promoted by Lewis and Brønsted acids, respectively. The reaction proceeds via a non-classical "bow-tie" cation which enables an uncommon 1,3-ring expansion of a cyclopropane to forge the bridged bicycle. We postulate that bow-tie type cations may be common among other 1,3-cyclopropane expansions. Notably, the reaction generates a highly reactive bridgehead olefin/cation which may be trapped intermolecularly by counterions or intramolecularly by arenes to generate bridged tetracycles. In the case of bridgehead chlorides, treatment with base provides a facile method for *in situ* regeneration of the anti-Bredt olefin which may be intercepted by exogenous nucleophiles.

We foresee the reaction having application in natural product synthesis. In particular, the reaction forges a variety of polycycles that map onto terpene natural products and incorporates several handles for subsequent modification. For instance, the intramolecular trapping products **30b-c** largely map onto the carbon framework of scopadulcic acid[54] while the ability to incorporate nitrogen at the bridgehead might allow the formation of the core aza-tetracycle found in annotine (Figure 2).[55-56] If the Nazarov-like cyclization of **27d-e** can be repeated with alkenes, it should also be possible to rapidly access terpenes such as zizaene.[57-58] Future efforts will examine the extension to substituted cyclopropanes, which will be required to enable the synthesis of these and other natural products, as well as the development of chiral catalysts capable of promoting the reaction in high enantioselectivity.

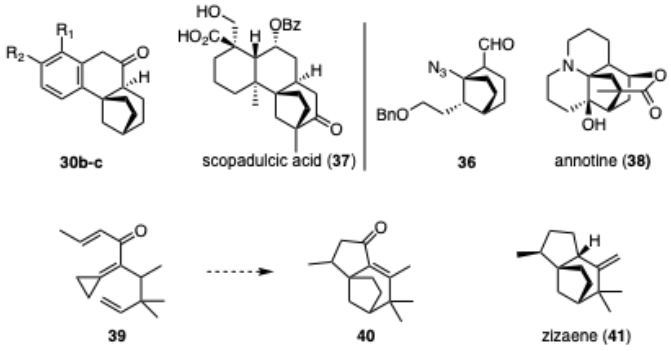


Figure 2: MACRO cyclization products and potential natural product targets.

Author contributions

A. R. I. and J. L. G. discovered and designed the project. A. R. I. developed the methodology, V. S. W. completed scope entries and product derivatizations. A. R. I. and J. L. G. completed computational analysis of the reaction. P. J. K. obtained and refined SCXRD data. A. R. I., V. S. W. and J. L. G. analysed the results and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Data availability

CCDC 2559237 contains the supplementary crystallographic data for compound **17e·DNPH**. The other data supporting this article have been included as part of the ESI.

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28. The use of Lewis acids was not applicable to aldehyde substrates. Treatment of 7d/e with aluminum chloride afforded intractable mixtures of products.
29. The use of Lewis acids ($AlCl_3$, $SnCl_4$) with **23a/b** was unsuccessful.
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