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[3,3] Ring Rearrangement of Oxo- or Aza-Bridged Bicyclo[3.2.1]octene-Based 1,5-Dienes

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Cite This: *Org. Lett.* 2021, 23, 2263−2267 Read Online

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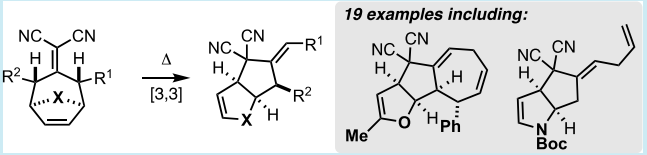
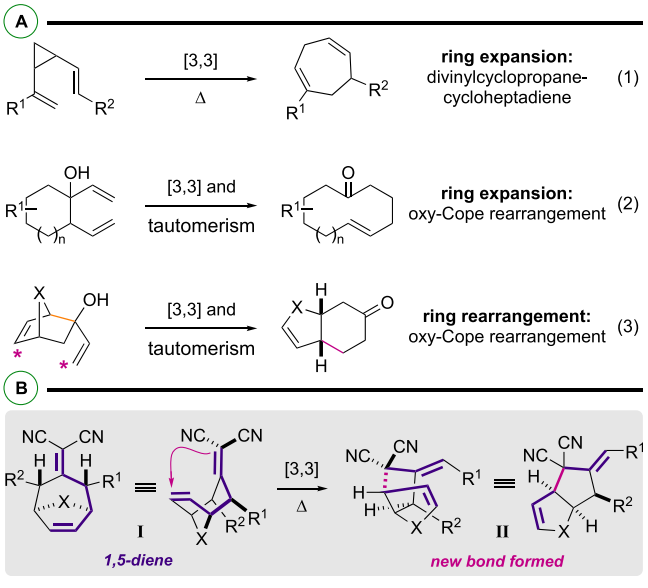
ABSTRACT: We report that oxo- or aza-bridged alkylidenemalononitrile-cycloheptenes undergo a [3,3] ring rearrangement to yield cyclopenta-fused dihydro-furans or pyrroles. Described herein are the origins of the serendipitous discovery, scope studies, and representative functional group interconversion chemistry.



The Cope rearrangement is a [3,3] allylic transposition reaction that proceeds via the concerted cleavage and reformation of C−C bonds.[1] Since its discovery 80 years ago,[2−4] the reaction has found considerable use in the synthesis of complex molecules,[5] including many recent methods and strategies.[6−19] One particular application of the Cope rearrangement is as a strategy for ring expansion[20−24] and rearrangement[25,26] transformations (Scheme 1A). For example, the divinylcyclopropane Cope rearrangement yields valuable cycloheptadienes whereby ring strain release provides a thermodynamic driving force (Scheme 1A, eq 1).[27−29] The oxy-Cope rearrangement is a highly valuable sigmatropic rearrangement that benefits from generally favorable thermodynamic profiles and substrates that are easily assembled.[25,26]

Scheme 1. (A) Summary of Cope Ring Expansions and Rearrangements and (B) This Report



Depending on the peripheral 1,5-diene structure, there are oxy-Cope-based ring expansions (Scheme 1A, eq 2) and ring rearrangements (Scheme 1A, eq 3). There are also Claisen [3,3] ring expansions and rearrangements.[30−35] Herein, we report the serendipitous discovery of a new class of 1,5-diene, bicyclo[3.2.1]octene alkylidenemalononitriles **I** that undergo Cope ring rearrangement to uniquely decorated *cis*-fused heteroatomic hexahydropentalenes **II** (Scheme 1B). Described are the origins of the discovery, studies related to the scope of the transformation, and representative functional group interconversion reactions.

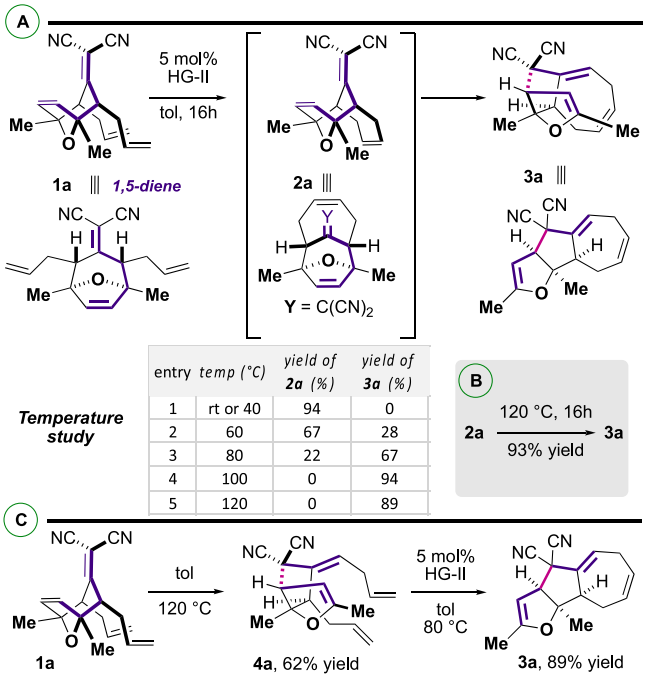
The ring rearrangement of bicyclo[3.2.1]octene alkylidenemalononitriles was first observed on **1a** (Scheme 2A). While attempting a ring-closing metathesis reaction,[36−38] it was found that the expected oxo- and alkylidenemalononitrile-bridged decadiene **2a** was observed with concomitant formation of **3a** with varying ratios/yields depending on the temperature (Scheme 2A). At room temperature to 40 °C, **2a** was the sole product and could be isolated in high yield (entry 1), whereas at temperatures ranging from 60−80 °C, mixtures of **2a** and **3a** were observed (entries 2 and 3). At further elevated temperatures (100−120 °C), **3a** was the sole product and could be isolated in high yield (entries 4 and 5). It is hypothesized that the unexpected product **3a** is arising via a Cope ring rearrangement from either **1a** or **2a**. In control experiments, it was found that both **1a** (Scheme 2C) and **2a** (Scheme 2B) are prone to the rearrangement when heated. Notably, **1a** rearranges to **4a** as a single alkene diastereomer, which can also undergo ring-closing metathesis to **3a**.

Knowing that the [3,3] ring rearrangement is favored at elevated temperatures, we next examined the scope of the

Received: February 1, 2021
Published: March 10, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00388
Org. Lett. 2021, 23, 2263−2267

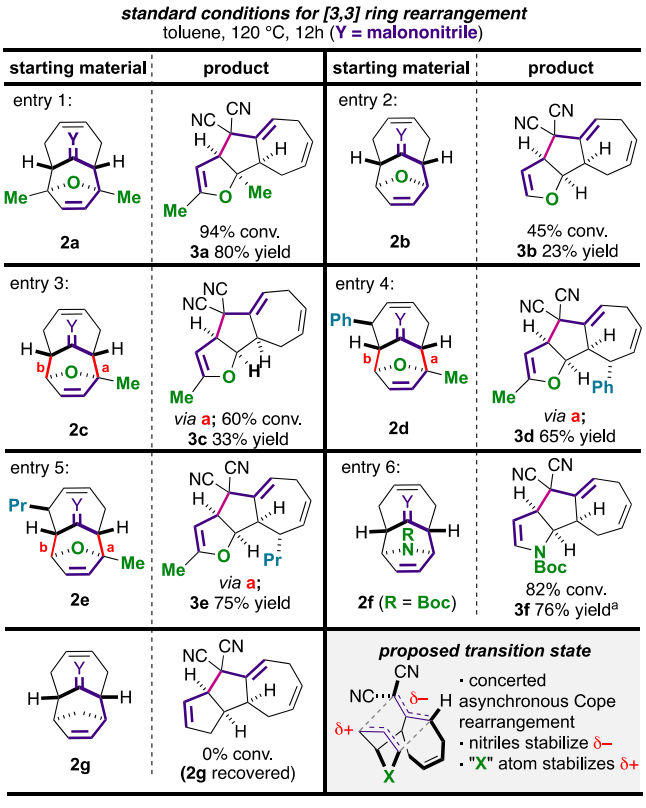
Scheme 2. (A) Initial Observations of a Ring-Open and Ring-Closed Scaffold Undergoing Cope Ring Rearrangement and (B, C) Both 2a and 1a Undergo [3,3] Ring Rearrangement



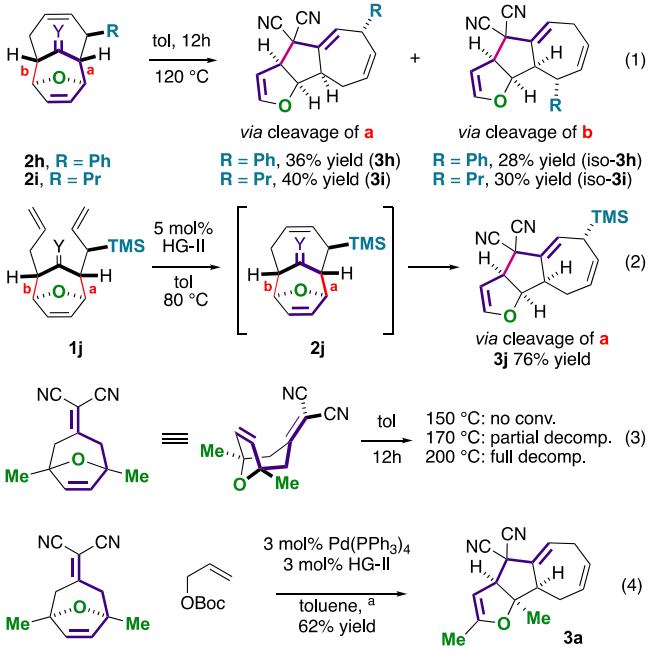
transformation using the ring-closed scaffolds **2a**–**2g** with a focus on key structural requirements for reactivity (Scheme 3). The starting materials (**2a**–**2g**) for this study are prepared via an iterative alkylation/Cope rearrangement/ring-closing metathesis sequence, which we recently described.[30] Substrates **2a**–**2e**, having various degrees of dihydrofuran methylation, were prepared to probe the significance of alkylation on reactivity, selectivity, and product stability. It was found that methylation at this position is important. Not only is there a trend linking methylation to reactivity and stability (entries 1 and 2), it was also observed that the monomethylated substrates **2c**–**2e** underwent regioselective transformation with C–C bond cleavage at the site bearing methylation. This selectivity was unaffected by additional peripheral decoration (**2d** and **2e**). That said, an aza-bridged scaffold **2f** lacking alkylation at the analogous position was a highly effective substrate, though it did require longer reaction time (48 h) to reach 82% conversion (Scheme 3, footnote a). Thus, there are likely numerous groups or combinations of groups that can be positioned to enhance the reactivity of the 1,5-diene substrate. Finally, **2g** having a methylene bridge was not reactive under the conditions examined. This study supports a concerted-asynchronous reaction pathway where the nitriles and the "X atom" serve to stabilize the developing negative and positive charge, respectively (see proposed transition state in Scheme 3).

We also looked at regioselectivity of more subtly differentiated substrates (Scheme 4, eqs 1 and 2). While substrates bearing peripheral aromatic (**2h**) and aliphatic (**2i**) substitution reacted efficiently, they did so without regioselectivity: There are few stereoelectronic differences between the pathways that involve the cleavage of bond "a" vs bond "b". Surprisingly, the silane-containing structure underwent regioselective Cope ring rearrangement during the ring-closing metathesis reaction (Scheme 4, eq 2). We do not yet fully understand the features yielding this regioselective result, though it could be that an increase in sterics (torsional strain) further weakens the bond that needs to break *via* [3,3]: the large, adjacent TMS group further weakens bond "a", thus

Scheme 3. Scope, Stereoelectronic Effects, and Summary of Key Features for the Cope Ring Rearrangement



Scheme 4. Miscellaneous Studies Related to the Scope of the Cope Ring Rearrangement Reaction



https://dx.doi.org/10.1021/acs.orglett.1c00388
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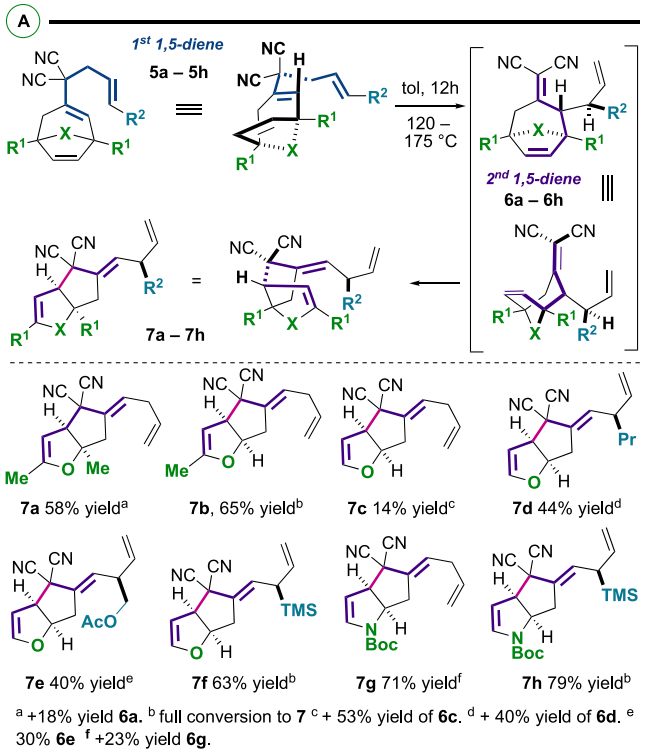
raising the ground state of **2j** and facilitating rearrangement. The Cope ring rearrangement was also attempted on an alkylidenemalononitrile lacking allylic groups (Scheme 4, eq 3). Upon heating the substrate in toluene from 150−200 °C, no rearrangement product was observed, and the material decomposed at higher temperatures. A possible explanation for the lack of reactivity is that in the absence of the allylic arms, the reactive conformer is less favored or the transformation in this case is thermodynamically unfavored. In either case, the allyl arms help bias the 1,5-diene toward the reactive [3,3] conformer. As a final miscellaneous result, it was found that a cascade reaction involving bis-allylation, Cope ring rearrangement, and olefin metathesis could directly yield the dihydrofuran−hydroazulene scaffold **3a** in a single step from the Knoevenagel adduct and allyl *tert*-butyl carbonate (Scheme 4, eq 4).

Many of the substrates in Schemes 3 and 4 are well-engineered to undergo the desired Cope ring rearrangement; their structures are rigid and locked in a conformer where the 1,5-diene termini are in proximity, and the substituents enforce an electronic pattern that promotes the desired transformation. Next efforts were aimed at identifying a simpler substrate class that undergoes this unique Cope ring rearrangement. In this regard, we explored a cascade sequence that converts 1,5-dienes **5** into a second 1,5-diene **6** that undergoes Cope ring rearrangement into heteroatomic hydropentalenes **7** (Scheme 5). Heterocyclic hydropentalenes are common pharmaceutical scaffolds (Figure 1). We were pleased to find that these "double Cope rearrangements" were generally successful. Many of the same trends are present from the previous studies on polycyclic scaffolds (Scheme 3). For example, furan methylation results in reasonably efficient Cope ring rearrangements (**7a** and **7b**); substrates lacking methylation are less reactive, and their products are less stable (**7c**) as significant decomposition was observed. When R^2 = alkyl, the second Cope rearrangement is less efficient, as determined by the isolated yields of **6d−e** to **7d−e**. Notably, when R^2 = TMS, there was complete conversion of **5f**/**6f** and good isolated yield of **7f**. The NBoc containing products **7g** and **7h** were also both isolated in good yields with ∼75% and complete conversion, respectively. Next, when using a substrate bearing a *Z*-olefin, we were able to prepare epimeric products, albeit with similarly modest conversions and yields (Scheme 5B) to the analogous furan systems described in Scheme 5A. We utilized substrate **5g** to examine the scalability of the iterative rearrangements (Scheme 5C). It was found that on near-gram scale, we could prepare 795 mg of **7g** (83% yield). This was achieved by resubjecting the isolated intermediate **6g** to thermal conditions.

In many of the cases examined thus far for [3,3] ring rearrangement (Schemes 4 and 5), conversion does not reach 100%. This suggests that either these reactions are slow (and require more time to proceed) or that [3,3] equilibrium has been reached. To probe this, we performed a time study for the transformation of **5a** → **6a** → **7a** and monitored the conversion by NMR (Scheme 6). It was found that the first Cope rearrangement (**5a** → **6a**) proceeds to 100% conversion within 2−3 h (entries 1−3) and that with continued heating the formation of **7a** increases until an equilibrium is reached that *does not exclusively favor* **7a** (entries 4−9). Thus, there is high thermodynamic favorably for the first rearrangement, likely driven forward by the establishment of alkylidenemalononitrile conjugation. There is a relatively minor change in ΔG from **6a** to **7a** (slightly exergonic in this case). The Cope ring rearrangement is likely driven forward by the release of ring-strain from the bridged bicyclic structure to the fused bicycle. This further suggests that the thermodynamic favorability for

Scheme 5. (A) Scope of the Double Cope (Ring) Rearrangement, (B) Example with *Z*-1,5-Diene, and (C) Scalability of the Transformation



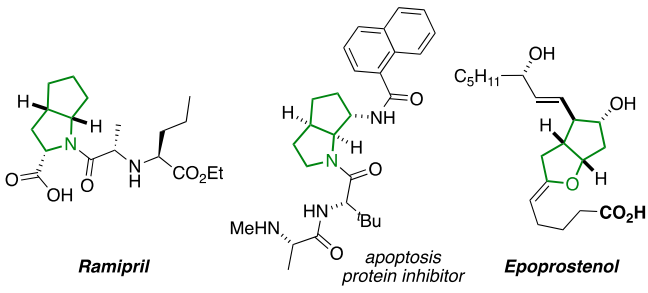


Figure 1. Representative heterocyclic hydropentalene pharmaceuticals.

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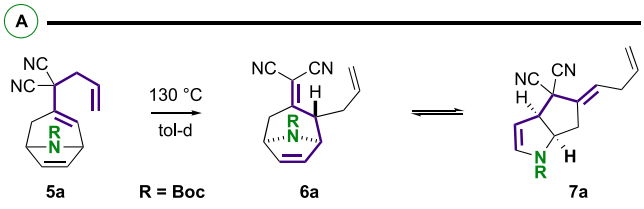
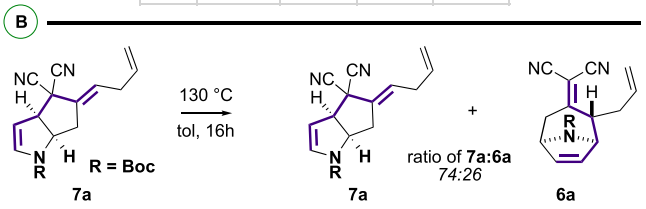
Scheme 6. (A) NMR Time Study of the Double Cope Rearrangement and (B) Scheme Showing the Fused Bicycle Is at Equilibrium with the Bridged Bicycle



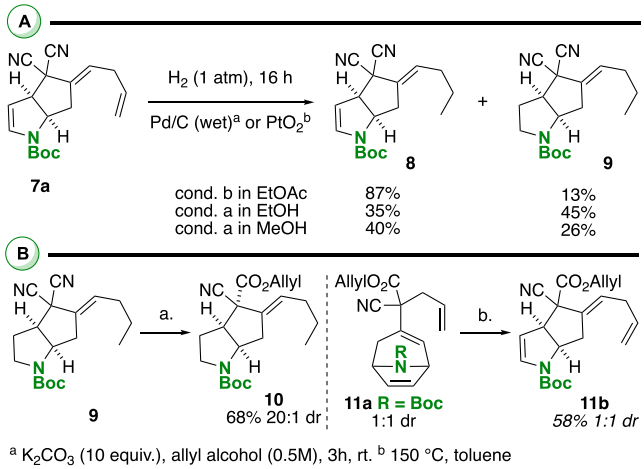
entry	time (h)	*5a* (%)	*6a* (%)	*7a* (%)
1	0.5	23	77	0
2	1	9	69	22
3	2	0	64	36
4	3	0	55	45
5	5	0	40	60
6	7	0	34	66
7	9	0	29	71
8	12	0	29	71
9	23	0	25	75



the other substrates in Scheme 5 may be similarly minor. Confirming this, it was found that the fused bicyclic product **7a** reverted to a 74:26 mixture of **7a**:**6a** (Scheme 6B).

This new Cope rearrangement represents a useful route to valuable scaffolds such as hydroazulenes (Schemes 3 and 4) and cyclopenta[*b*]pyrrolidines and furans (Scheme 5) bearing unique functional groups for interconversion. As such, our final studies were to briefly examine some transformations on the scaffolds (Scheme 7). We found that on **7a**, the alkene and the enamine can be coreduced via standard hydrogenation conditions. While the monosubstituted alkene is readily hydrogenated (**8**), the enamine reacts slower (**9**). Next, the malononitrile can be converted into a cyanoacetate by Pinner reaction/hydrolysis, yielding **10**. Notably, we also found that

Scheme 7. Scaffold Transformations



[a] K_2CO_3 (10 equiv.), allyl alcohol (0.5M), 3h, rt. [b] 150 °C, toluene

cyanoacetate-containing scaffolds **11b** can also be established via double Cope ring rearrangement from **11a**.

We have uncovered that oxo- or aza-bridged alkylidenemalononitrile-cycloheptenes undergo a Cope ring rearrangement reaction. This transformation was shown to yield tricyclic dihydrofuran−hydroazulenes (Schemes 3 and 4) or cyclopenta−dihydrofurans or pyrroles (Scheme 5) in a range of yields and conversions, likely due to minimal changes in thermodynamic preference. Also shown was a model sequence for preparing potentially valuable cyclopenta[b]pyrroles that bear unique functionality for interconversion chemistry. Future directions are manyfold and include addressing thermodynamics to render the sequence more favorable, asymmetry to yield enantioenriched building blocks, and synthetic applications, especially toward the privileged cyclopenta[b]pyrrolidine chemical space.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00388.

Experimental procedures; compound characterization (^{1}H NMR, ^{13}C NMR, and HRMS); copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant No. 1844443. We thank the College of Liberal Arts and Sciences and the Department of Chemistry at the University of Florida for start-up funds. We thank Umicore for the generous donation of metathesis catalysts. We thank the Mass Spectrometry Research and Education Center and their funding source: NIH S10 OD021758-01A1. This work is dedicated to Dr. William B. Martin in appreciation of his incredible mentorship to E.S. and A.J.G.

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Org. Lett. 2021, 23, 2263−2267