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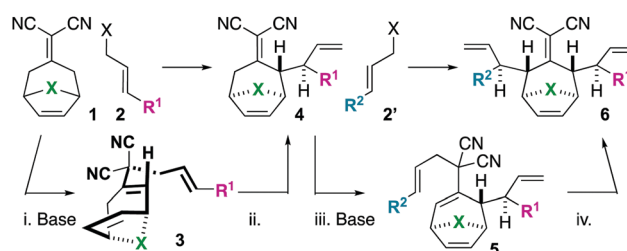
Selective ring-rearrangement or ring-closing metathesis of bicyclo[3.2.1]octenes†

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Explored was the competitive ring-closing metathesis vs. ring-rearrangement metathesis of bicyclo[3.2.1]octenes prepared by a simple and convergent synthesis from bicyclic alkylidenemalononitriles and allylic electrophiles. It was uncovered that ring-closing metathesis occurs exclusively on the tetraene-variant, yielding unique, stereochemically and functionally rich polycyclic bridged frameworks, whereas the reduced version (a triene) undergoes ring-rearrangement metathesis to 5-6-5 fused ring systems resembling the isoryanodane core.

3,3-Dicyano-1,5-dienes are attractive substrates due to their ease of construction from ketones, malononitrile, and allylic electrophiles, and their ability to undergo Cope rearrangement.¹ In fact, 3,3-dicyano-1,5-dienes are the classic Cope rearrangement substrates.² We have been studying this class of 1,5-dienes as substrates for complex polycycloalkane synthesis.^{3–7}

We became interested in iterating the deconjugative alkylation^{8–10} and the diastereoselective[3,3]sigmatropic rearrangement steps of alkylidenemalononitrile functionalization. If performed on alkylidenemalononitriles **1** with allylic electrophiles **2/2'**, unique tetraenes **6** could be rapidly established *via* intermediates **3–5** (Scheme 1). Further piquing our interest was how these substrates would react under olefin metathesis conditions: would they undergo ring-closing metathesis (RCM¹¹) (to **7**) or ring-rearrangement metathesis (RRM¹²) (to **8**) (Scheme 2A)? ring-rearrangement metathesis would occur by the ring-opening of the central, strained cycloheptene olefin followed by double ring-closing metathesis, whereas ring-closing metathesis would result simply from the “allyl arms” reacting with each other directly. Notably, the ring-closing route would require the “allyl arms” to be *cis*-oriented^{13–16} as well as a conformationally biased¹⁷ for the axial isomer. In addition to the growing body of work on the synthesis of bridged bicyclic systems *via* RCM,^{13–16} we have previously



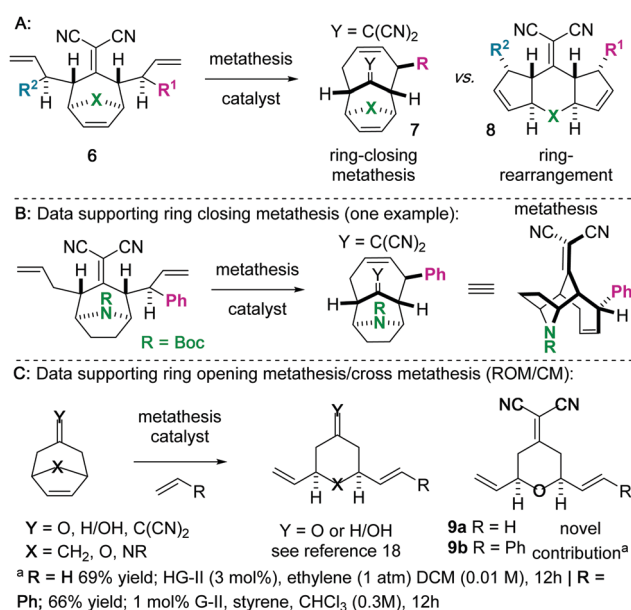
Scheme 1 Iterative deconjugative allylation/Cope rearrangement to synthesize bicyclic tetraenes (**6**).

shown one example of an RCM reaction on a scaffold related to those of interest to this work,⁶ though there are no possibilities for RRM with this particular substrate (Scheme 2B). Conversely, bridged bicyclo[3.2.1]octenes can react by ring-opening cross-metathesis (ROCM) or polymerization (ROMP) (Scheme 2C).^{18–21} For example, ketone (Y = O), alcohol (Y = H/OH), and alkylidenemalononitrile-containing scaffolds react *via* ROCM (Scheme 2C). Thus, we hypothesize that either pathway (RCM or RRM) is plausible and potentially in competition for the proposed scaffolds **6**. As such, we began a campaign to explore the reactivity and selectivity of these types of substrates in RCM *vs.* RRM reactivity. Herein we report that such tetraenes **6** undergo exclusive ring-closing metathesis to **7**. We also provide a hypothesis for the observed chemoselectivity, which ultimately yields a method to achieve exclusive ring-rearrangement metathesis to 5-6-5 tricyclic ring systems.

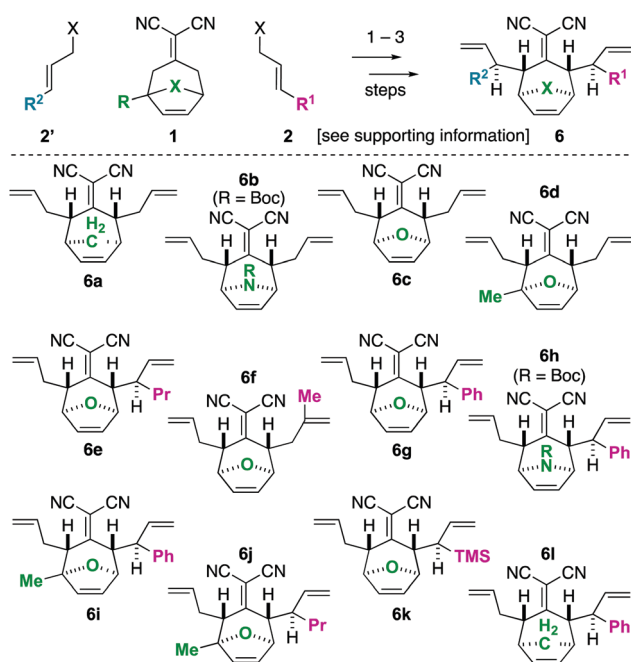
To begin our studies, we prepared tetraenes **6a–6l** by iterative deconjugative allylic alkylation/Cope rearrangement (Scheme 3). Depending on the substitution pattern, products **6** are available in 1–3 steps as single diastereomers *via* diastereoselective Cope rearrangements (see the ESI[†]). We next turned to the examination of the ring-closing metathesis (RCM) *vs.* ring-rearrangement metathesis (RRM) question posed for these substrates (Scheme 4). In these studies, standard Ru-based metathesis catalysts (Grubbs-II²² (G-II) or Hoveyda–Grubbs-II²² (HG-II)) were utilized. Substrates **6a–6l** underwent clean ring closing metathesis to **7a–7l** exclusively under conventional conditions (*e.g.* nonpolar solvent,

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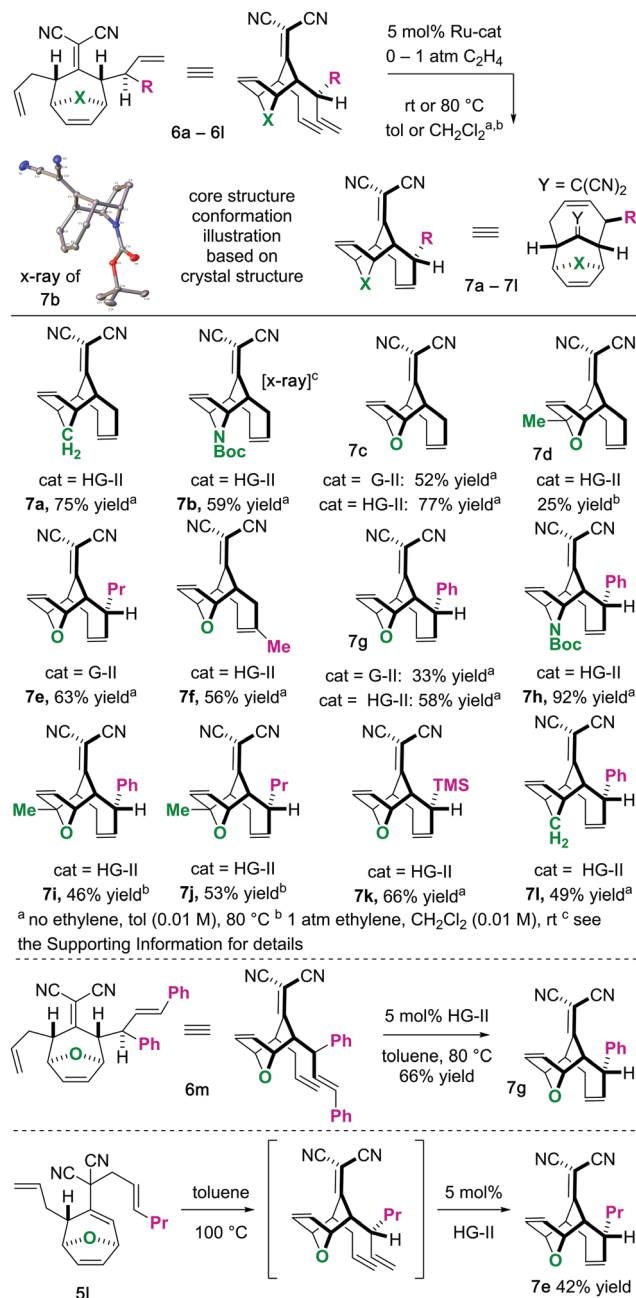


Scheme 2 (A) Will bicyclic tetraenes **6** undergo RCM or RRM? (B–C) Support for RCM and RRM.



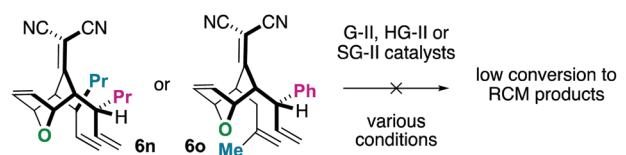
Scheme 3 Synthesis of bicyclic tetraenes.

r.t. –80 °C, with or without ethylene). Generally speaking, both catalysts examined performed reasonably well. However, in a few side-by-side comparisons, the HG-II catalyst did outperform the G-II catalyst. The first three products in the table (**7a–7c**) were either cyclopentadiene (**7a**), *N*-Boc-pyrrole (**7b**), or furan (**7c**) derived. For these substrates, the methylene or heteroatom “X-group” had little to no effect on the efficiency of the transformation. The remaining substrates **6d–6l** showcase a variety of substitution patterns and functional groups that were tolerated in the ring-closing metathesis reaction yielding **7d–7l**. We also found

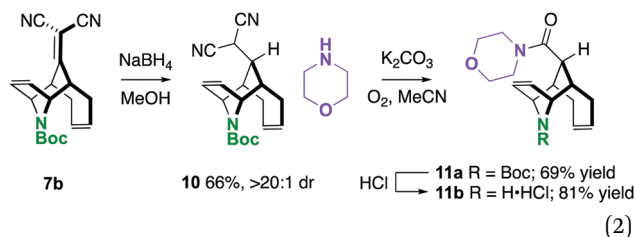


Scheme 4 Scope of ring-closing metathesis reaction.

that the 1,3-diphenylallyl moiety on **6m** performed well in the metathesis reaction to yield **7g** (Scheme 4). As a final note, preliminary data supports that the sequence can be telescoped: from **5l**, the Cope rearrangement and the ring-closing metathesis steps can be performed in one-pot fashion to yield **7e**.



(1)



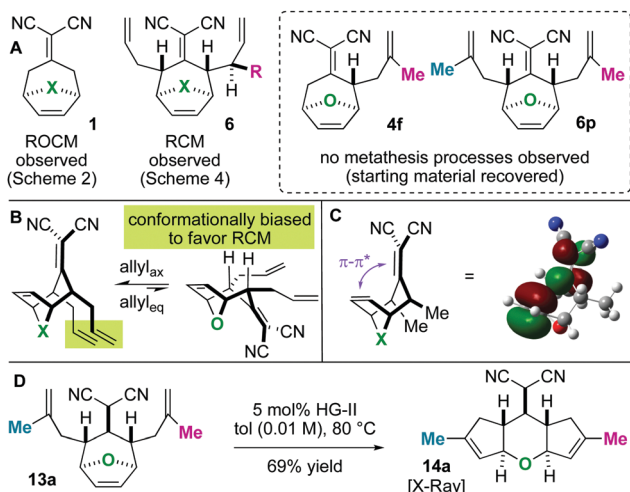
For the substrates in Scheme 4 only one of the “allylic arms” is decorated with an additional substituent. That is because it is generally challenging to perform ring-closing metathesis on densely substituted alkenes. For example, substrates **6n** and **6o** underwent sluggish and low yielding ring-closing metathesis, even with the Stewart–Grubbs (SG-II; CAS#: [927429-61-6]²³) catalyst, which is commonly more accepting to steric challenges (eqn (1)).

One way in which we envisaged finding potential application of these molecules is described in Scheme 5. In two steps, a unique piperidine carboxamide **11a** was prepared by NaBH₄ conjugate reduction and oxidative amidation.²⁴ The *N*-Boc-piperidine can be deprotected to the amine-HCl **11b** under standard conditions resulting in an interesting scaffold for drug discovery, considering that they are rigid piperidine carboxylate scaffolds.²⁵

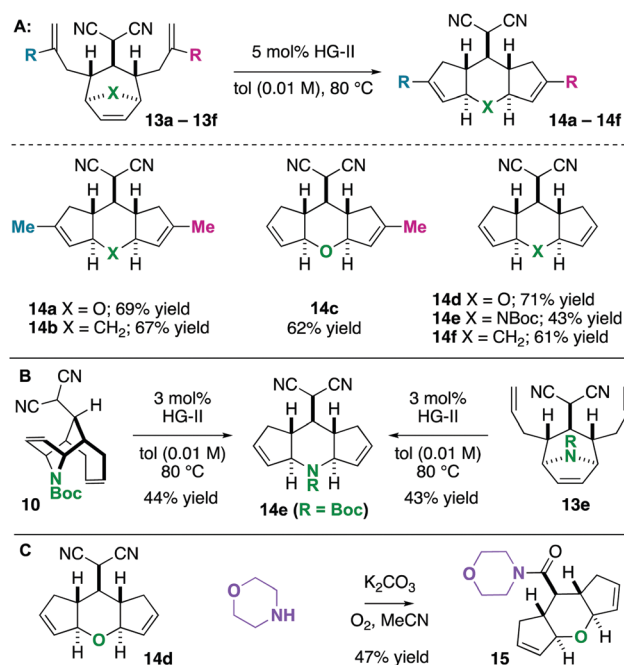
Next, we wished to understand and overturn the observed chemoselectivity for ring-closing metathesis over ring-rearrangement metathesis (Scheme 5). To compare and summarize, non-allylated (**1**) and bis-allylated (**6**) scaffolds have unique reactivity to metathesis catalysts: scaffolds **1** undergo ring-opening cross metathesis (ROCM) whereas the bis-allylated variants undergo ring-closing metathesis (RCM). A thought-provoking observation was that **6p** was wholly unreactive to metathesis catalysts. Regarding **6p**, we presumed that ring-closing metathesis to yield a tetrasubstituted olefin would be unfavourable and therefore ring-rearrangement metathesis would be the dominant

pathway. However, no metathesis processes were observed; the starting material was recovered in high yield. Furthermore, even the mono 2-methylallylated scaffold **4f** was completely unreactive (starting material recovered). These observations allow us to draw conclusions on the ring-closing vs. ring-rearrangement metathesis chemoselectivity (Scheme 5B and C). First, ring-closing metathesis is favoured when either di- or tri-substituted cyclic olefins are expected. The structures are also conformationally biased, where the “allylic arms” are in an axial-position and thus in close proximity to one another (Scheme 5B). This was confirmed by NMR studies (see the ESI[†]). And second, as shown in Scheme 5C, we have found an anchimeric effect between the cyclic alkene and the alkylidene-malononitrile (a π - π^* interaction). This was achieved computationally where structures were optimized using the DFT level of theory M062x/cc-pvdz.²⁶ Notably, the qualitative trends do not change when using a different functional or basis set combination. We found the localized bond orbitals for the π and π^* orbitals of interest, and used the second order energy between them as computed in NBO 3.1 to quantify the extent of the interaction. Specifically, a 1.9 kcal mol⁻¹ interaction energy was found. To remove this through space interaction (anchimeric effect), the alkylidenemalononitrile was reduced yielding **13a**, which exclusively underwent ring-rearrangement metathesis to **14a** (Scheme 5D).

Having found that ring-rearrangement metathesis can be favoured by alkylidenemalononitrile reduction, we next examined the scope of the RRM transformation (Scheme 6). It was found that a variety of scaffolds with 2-alkylation on the “allylic arms” were competent substrates for ring-rearrangement (**14a-c**). We expected these substrates to be successful because ring-closing



Scheme 5 (A) Summary of RCM vs. RRM selectivity. (B and C) Rationale for RCM regioselectivity: conformational bias (B) and an anchimeric effect (C). (D) Alkylidene reduction results in a scaffold that undergoes ring-rearrangement metathesis.



Scheme 6 (A and B) Ring rearrangement metathesis to 5-6-5 scaffolds. (C) Oxidative amidation.

metathesis is prohibited by the substitution patterns on the alkenes. We were pleased to also find that substrates with unsubstituted “allylic arms” also yielded the desired ring-rearrangement metathesis products **14d–14f** over the ring-closing metathesis products. It was also observed that **14e** could be prepared either from a linear precursor **13e** or a cyclic one **10**, prepared independently *via* the chemistry described in Scheme 6. Thus, there are two potential entry routes into the ring-rearranged 5-6-5 scaffolds. As a final result, the malononitrile functional group can be interconverted to amides by Hayashi's oxidative amidation protocol as shown in the conversion of **14d** to **15**.

We have developed a protocol to assemble bicyclic[3.2.1]-tetraenes and explored their reactivity as metathesis substrates. It was uncovered that the tetraenes are kinetically predisposed to undergo ring closing metathesis yielding doubly bridged cyclodeca-1,6-dienes. It was also hypothesized that a π - π^* interaction between the strained endocyclic olefin and the alkylidenemalononitrile precluded ring-opening metathesis. In support of this hypothesis, alkylidenemalononitrile reduction can result in chemoselectivity favouring ring-rearrangement metathesis. For both of the scaffolds, the malononitrile functional group can be converted to amides by oxidative amidation. Future studies will involve the exploration of transformations favouring ring-rearrangement metathesis, as this yields frameworks common to natural products such as pepluanone,^{27,28} retigeranic acid,²⁹ perseanol,³⁰ and leucosceptroids,^{31–33} among others.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 E. A. Ildardi, C. E. Stivala and A. Zakarian, *Chem. Soc. Rev.*, 2009, **38**, 3133–3148.
- 2 A. C. Cope and K. E. Hoyle, *J. Am. Chem. Soc.*, 1941, **63**, 733–736.

- 3 F. Emmetiere and A. J. Grenning, *Org. Lett.*, 2020, **22**, 842–847.
- 4 P. Vertesaljai, R. Serrano, M. D. Mannchen, M. Williams, E. Semenova and A. J. Grenning, *Org. Lett.*, 2019, **21**, 5704–5707.
- 5 E. Fereyduni, J. N. Sanders, G. Gonzalez, K. N. Houk and A. J. Grenning, *Chem. Sci.*, 2018, **9**, 8760–8764.
- 6 E. Fereyduni and A. J. Grenning, *Org. Lett.*, 2017, **19**, 4130–4133.
- 7 O. Lahtigui, F. Emmetiere, W. Zhang, L. Jirmo, S. Toledo-Roy, J. C. Hersberger, J. M. Macho and A. J. Grenning, *Angew. Chem., Int. Ed.*, 2016, **55**, 15792–15796.
- 8 H. Nakamura, H. Iwama, M. Ito and Y. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 10850–10851.
- 9 R. B. Grossman and M. A. Varner, *J. Org. Chem.*, 1997, **62**, 5235–5237.
- 10 P. Vertesaljai, P. V. Navaratne and A. J. Grenning, *Angew. Chem., Int. Ed.*, 2016, **55**, 317–320.
- 11 M. E. Maier, *Angew. Chem., Int. Ed.*, 2000, **39**, 2073–2077.
- 12 S. Kotha, M. Meshram, P. Khedkar, S. Banerjee and D. Deodhar, *Beilstein J. Org. Chem.*, 2015, **11**, 1833–1864.
- 13 A. Morehead Jr. and R. Grubbs, *Chem. Commun.*, 1998, 275–276.
- 14 C. E. Neipp and S. F. Martin, *J. Org. Chem.*, 2003, **68**, 8867–8878.
- 15 A. Michaut, S. Miranda-Garcia, J. C. Menendez and J. Rodriguez, *Org. Lett.*, 2004, **6**, 3075–3078.
- 16 M. Lin, P.-J. Cai, Z. Zeng, N. Lin, Y. Shen, B. Tang, F. Li, C. Chen, Z.-X. Yu and Y. Zhang, *Chem. – Eur. J.*, 2018, **24**, 2334–2338.
- 17 R. Chen, Y. Shen, S. Yang and Y. Zhang, *Angew. Chem., Int. Ed.*, 2020, **59**, 14198–14210.
- 18 D. L. Wright, L. C. Usher and M. Estrella-Jimenez, *Org. Lett.*, 2001, **3**, 4275–4277.
- 19 M. D. Mihovilovic, B. Groetzl, W. Kandioller, R. Snajdrova, A. Muskotal, D. A. Bianchi and P. Stanetty, *Adv. Synth. Catal.*, 2006, **348**, 463–470.
- 20 J. Mandel, N. Dubois, M. Neuburger and N. Blanchard, *Chem. Commun.*, 2011, **47**, 10284–10286.
- 21 P. Disetti, L. Piras, M. Moccia, M. Saviano and M. F. A. Adamo, *Eur. J. Org. Chem.*, 2017, 6202–6208.
- 22 M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.
- 23 I. C. Stewart, T. Ung, A. A. Pletnev, J. M. Berlin, R. H. Grubbs and Y. Schrodi, *Org. Lett.*, 2007, **9**, 1589–1592.
- 24 J. Li, M. J. Lear and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2016, **55**, 9060–9064.
- 25 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- 26 See the ESI† for details related to this computational analysis.
- 27 G. Corea, E. Fattorusso, V. Lanzotti, P. Di Meglio, P. Maffia, G. Grassia, A. Ialenti and A. Ianaro, *J. Med. Chem.*, 2005, **48**, 7055–7062.
- 28 E. Barile, E. Fattorusso, A. Ialenti, A. Ianaro and V. Lanzotti, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4196–4200.
- 29 M. Kaneda, R. Takahashi, Y. Iitaka and S. Shibata, *Tetrahedron Lett.*, 1972, **13**, 4609–4611.
- 30 A. Han, Y. Tao and S. E. Reisman, *Nature*, 2019, **573**, 563–567.
- 31 C. L. Hugelshofer and T. Magauer, *J. Am. Chem. Soc.*, 2015, **137**, 3807–3810.
- 32 C. L. Hugelshofer and T. Magauer, *Angew. Chem., Int. Ed.*, 2014, **53**, 11351–11355.
- 33 S. Guo, J. Liu and D. Ma, *Angew. Chem., Int. Ed.*, 2015, **54**, 1298–1301.