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Controlling, understanding, and redirecting the thermal rearrangement of 3,3-dicyano-1,5-enynes

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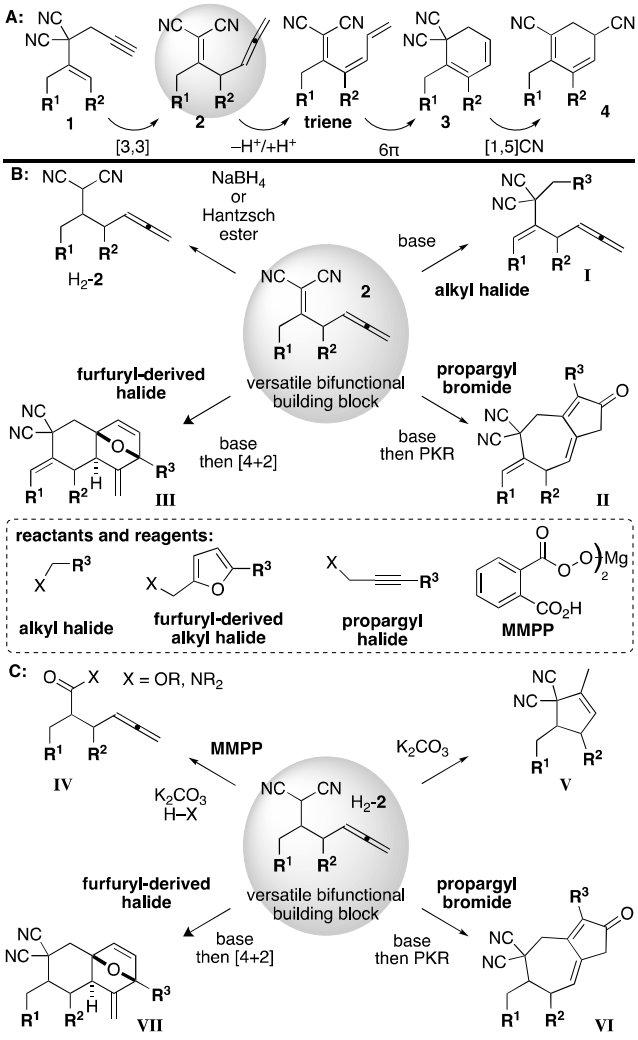
Supporting Information Placeholder

ABSTRACT: The thermal [3,3] rearrangement of 3,3-dicyano-1,5-enynes to γ-allenyl alkylidenemalononitriles (the "enyne Cope rearrangement") has largely eluded synthetic value as the desired products, too, are thermally reactive and ultimately yield 6π electrocyclization products. Herein, we describe experimental and computation studies related to the thermal rearrangement of 1,5-enynes, structural features to halt the thermal rearrangement at the allene-stage, and a reductive variant for preparing bifunctional allenyl malononitriles. We also describe various ways that the bifunctional building blocks can be manipulated and converted to cyclic and acyclic architectures.

INTRODUCTION

Thermal rearrangement of 3,3-dicyano-1,5-enynes can yield a suite of products (Scheme 1A).[1] In cascade fashion, they undergo [3,3] sigmatropic rearrangement to γ-allenyl alkylidenemalononitrile **2**, "proton transfer" to the triene, 6π-electrocyclization to **3**, and [1,5]CN shift to **4**. This thermal sequence was originally reported by Roger Brown and co-workers with little exploration of optimization or scope.[1] Although many of the products **2** – **4** likely have synthetic value, we are interested in the allenyl intermediate **2**, which bears a reactive alkylidenemalononitrile and allene. Generally speaking, the enyne Cope rearrangement, also known in the literature as the acetylenic Cope rearrangement or the propargyl Cope rearrangement, has only a few reports including physical organic studies,[2] a retro-variant,[3] and theoretical studies.[4] Notably, the [3,3] rearrangement of propargyl enol ethers (the "propargyl Claisen rearrangement") has seen considerable application in modern synthesis.[5]

Scheme 1. A: Thermal rearrangement of 3,3-dicyano-1,5-enynes. B and C: The allenyl intermediate "2" and its reduced counterpart "H_2-2" are attractive bifunctional building blocks.



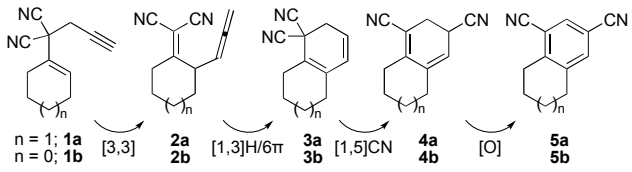
We are interested in applying the enyne Cope rearrangement of 3,3-dicyano-1,5-enynes **1** to complex molecule synthesis.[6] Enynes **1** are readily constructed from

ketones, malononitrile, and propargyl bromides, which allows for significant substrate diversity. If the products **2** are rendered highly accessible by the Cope rearrangement of enynes **1**, a vast array of chemical space can be easily accessed by standard chemistry (Scheme 1B). For example, alkylidenemalononitriles undergo mild reduction (*e.g.* to H_2-**2**)[7] or can be alkylated by deconjugative alkylation (*e.g.* to **I**).[6] Attractively, **2** are *bifunctional* in that they can undergo mild deconjugative alkylation then cyclization with propargyl bromides or furfuryl-derived alkyl halides to yield hydroazulenes **II**[8] or decalins **III**[9], respectively, in two steps. The reduced counterparts H_2-**2** also have some unique and noteworthy reactivity (Scheme 2C). *Mono*-alkylmalononitriles undergo oxidative decyanation to yield esters or amides **IV**.[10] It has also been found that these building blocks undergo a mild-base catalyzed cycloisomerization to cyclopentenes **V**.[11] Additionally, deconjugative alkylation/cyclization, similar to as described for **2,** can yield common natural product frameworks (**VI – VII**). The major limitation is accessing these versatile building blocks *via* the enyne Cope rearrangement because, as described above, the thermal reaction results in various products (**2** – **4**, Scheme 1A). This is the primary contributor to the modest yields of γ-allenylalkylidenemalononitriles. Considering the potential value of the enyne Cope rearrangement of 3,3-dicyano-1,5-enynes to synthesis, we wished to better understand the transformation and improve its scope, efficiency, and applicability, which is described herein.

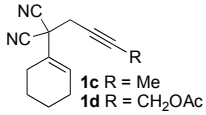
THERMAL TRANSFORMATION OF SIMPLE, MODEL 3,3-DICYANO-1,5-ENYNES

As noted in previous work from Brown,[1] our own studies,[6] and further explored herein, the thermal rearrangement of **1a** begins to occur at temperatures above ~110 °C. We first evaluated the effect of time on the product distribution (Scheme 2, entries 1 and 2). The allene is favored at shorter reaction times (entry 1); however, as the heating time is increased, the reaction proceeds to favor the electrocyclization products (entry 2). We saw similar results with the five-membered ring variant (**1b**, entries 3 – 5). In trace amounts, we also observed products of auto-oxidation to the benzodinitriles **5** in these studies. Brown and co-workers noted significantly more benzenoid formation under their conditions (200 °C). Furthermore, we found that the acidic additive trifluoroethanol (TFE) helped promote the proton transfer step as well as the [1,5]CN shift. In a similar fashion, we also examined the 1,5-enyne **1c** and **1d** bearing an internal alkyne. Under analogous conditions (150 °C, toluene), no reaction occurred, indicating a high barrier to [3,3] rearrangement. When increasing the temperature, conversion began to occur, but in no cases were allenes observed. This is likely because the additional energy necessary for the [3,3] also facilities the additional isomerizations.

Scheme 2. Thermal cascade reaction of 3,3-dicyano-1,5-enynes.



entry	n (1a/b)	Solvent	Temp (°C)	Time (h)	% conv.	2	3	4	5
1	1 (**1a**)	tol	130	6	59	95	<5	<5	<5
2	1 (**1a**)	tol	130	24	95	36	25	39	<5
3	0 (**1b**)	tol	130	6	90	42	32	26	<5
4	0 (**1b**)	tol	130	24	>95	<5	64	36	<5
5	0 (**1b**)	tol:TFE (5:1)	130	6	72	<5	42	58	<5



1c R = Me
1d R = CH_2OAc

reaction conditions: toluene, 0.1M, 2h

temperature variable:
150 °C: <05% conv.
180 °C: ~50% conv.[a]
200 °C; ~95% conv.[b]

results: [a] complex mixtures observed, trace allene signals in crude NMRs
[b] complex mixtures observed, no allene signals in crude NMRs

COMPUTATIONAL ANALYSIS OF THE [3,3] REARRANGEMENT OF MODEL 3,3-DICYANO-1,5-ENYNES

We next turned to computation and performed state-of-the-art density functional theory computations to better understand the sigmatropic rearrangement step (Figure 1). Our main finding was that the enyne Cope rearrangement is sensitive to whether the starting alkyne is terminal or internal. In particular, we computed a free energy barrier of 31.5 kcal/mol for the parent terminal alkyne **1a**, but larger barriers of 33.6 kcal/mol and 33.5 kcal/mol respectively for the related internal alkynes **1c** and **1d**. The breaking and forming bonds in the internal alkyne transition states were approximately 0.1 Å longer than in the terminal alkyne transition state, suggesting that the higher barrier comes from steric hindrance that prevents the enyne termini from approaching each other as closely. This computational result is consistent with the experimental finding that internal alkynes require higher temperatures for the Cope rearrangement, making them more prone to rearrangement through the pathway shown in Scheme 1A.

We found a similar trend with bicyclic scaffolds (Figure 1), with internal alkynes **1f** and **1g** having free energy barriers that were 1-2 kcal/mol higher and bond lengths that were ~0.1 Å longer than terminal alkyne **1e**. However, as compared to the monocyclic scaffolds, the bicyclic scaffolds exhibit a lower free energy barrier, and computations reveal that this is due to a raised ground state that possesses significant torsional strain. As shown in Figure 2, the bicyclic scaffold **1e** requires the starting material to adopt a near-eclipsed conformation with an illustrated HCCH dihedral angle of 19.6 degrees. This high-energy dihedral angle is subsequently relaxed to 39.7 degrees in the transition state (and 61.8 degrees in the product). In contrast, monocyclic starting material **1a** has a corresponding dihedral angle of 44.2 degrees,

so it is not significantly destabilized and consequently has a higher free energy barrier for the enyne Cope rearrangement.

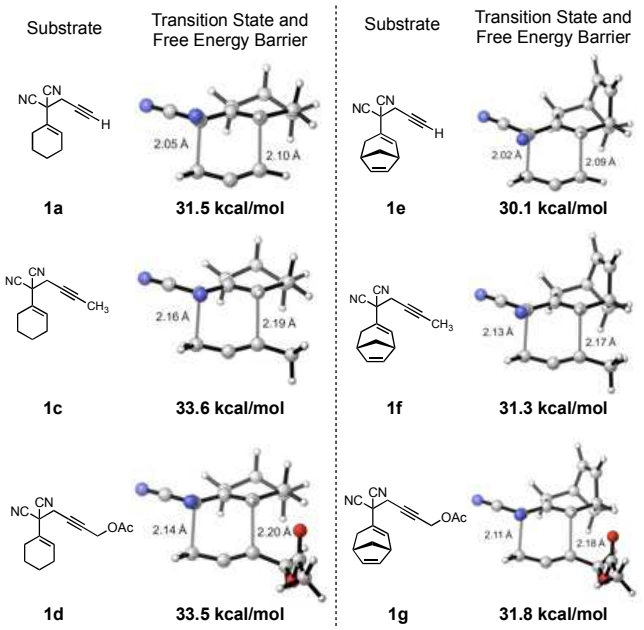


Figure 1. Free energy barriers for the enyne Cope rearrangement of terminal and internal alkynes.

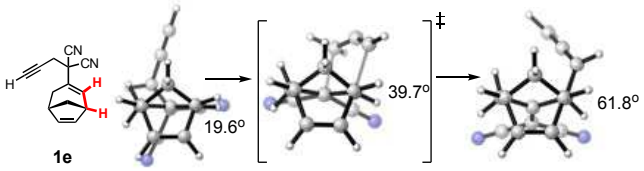


Figure 2. In bicyclic scaffold 1e, the illustrated HCCH dihedral angle increases from 19.6 degrees in the starting material to 39.7 degrees in the transition state and 61.8 degrees in the product.

Because some allene products undergo further reaction (Scheme 2), we performed a conformational study of product allene **2a** formed from terminal alkyne **1a**. As shown in Figure 3, the axial conformation of the allene formed directly in the Cope rearrangement is more stable than the equatorial conformation by 2.8 kcal/mol. The equatorial conformation suffers from allylic strain between the allene and alkylidenemalononitrile moieties, which is alleviated by having the allene eclipse the axial γ-C–H bond. Nevertheless, the equatorial conformation of the allene is readily accessible via a chair-chair interconversion under the reaction conditions. We hypothesize that this conformation is critical to decomposition because the axial γ-C–H bond is aligned with the π system of the alkylidenemalononitrile for deprotonation and, therefore, further reaction. In contrast, in the bicyclic systems **1e**, **1f**, and **1g**, the allene is locked in the axial conformation and the γ-C–H bond is orthogonal to the π system of the alkylidenemalononitrile, so no further reaction can occur.

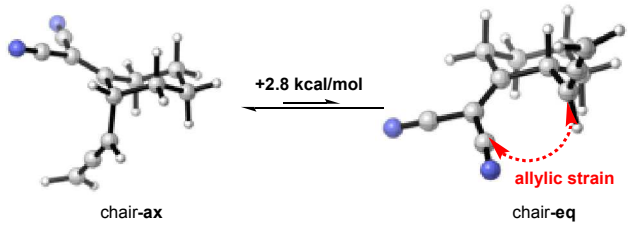


Figure 3. The axial conformation of allene 2a is more stable than the equatorial conformation by 2.8 kcal/mol.

Based on the above experimental and computational data, we have come to the following conclusions:

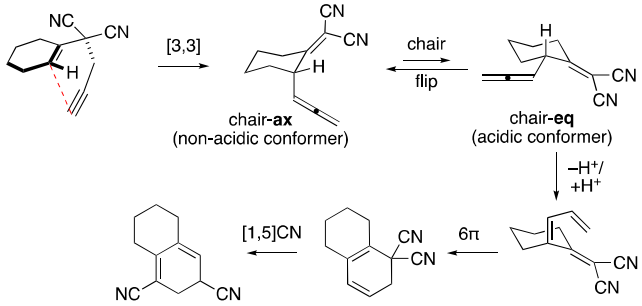
(1) The transformation is sensitive to steric effects at the enyne *termini*. Experimentally, internal alkynes require higher temperature and therefore decompose unless structural features are present which prevent access to the reactive conformer. This is supported by the computational studies showing a ~2 kcal/mol difference in transition state energy between terminal alkyne **1a** and internal alkynes **1c** and **1d**.

(2) The bicyclic scaffolds examined have a lower activation energy as a result of a destabilized ground state.

(3) The allene prefers to be axial, which minimizes allylic strain between the alkylidenemalononitrile and the allene.

(4) Restricting conformations post [3,3] rearrangement can preclude the proton-transfer step (and therefore downstream rearrangements) resulting in higher yields of the targeted allenes. This is because the γ-C–H bond is more readily deprotonated when it is aligned with the alkylidenemalononitrile π system.

Scheme 3. Detailed mechanism for thermal rearrangement



This computational data supports the following mechanism for thermal cascade rearrangement (Scheme 3): [3,3] rearrangement occurs to yield the chair conformer having the allene axial (chair-**ax**). This conformer must undergo a chair-chair interconversion to the equatorial allene conformer (chair-**eq**), the acidic conformer, to allow for proton transfer to the triene, followed by electrocyclization and 1,5[CN] shift.

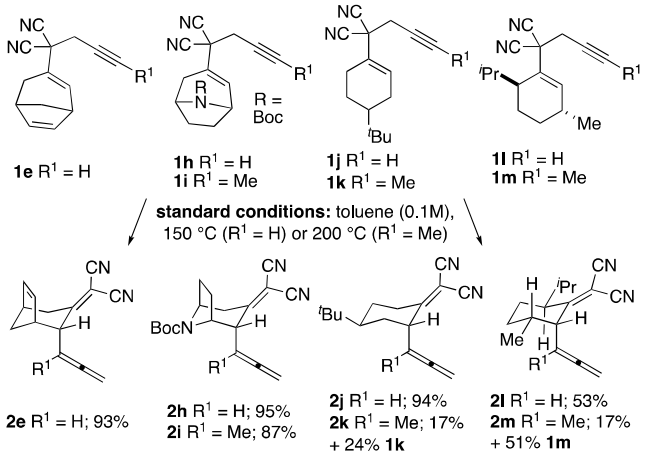
The above computational discoveries set the stage for new hypotheses aimed at improving the scope of allene synthesis by [3,3] rearrangement. Specifically, we

wished to identify substrate classes that would stop thermally rearranging prior to allene isomerization as well as devise a protocol to prepare allenes by this method that is *not* tied to substrate structure. These are the subjects of the following two sections, respectively.

PREVENTING THE THERMAL CASCADE THROUGH SUBSTRATE STRUCTURE BIAS

We suspected that certain substructures could be incorporated onto the 1,5-enyne to prevent the proton transfer step, thus preventing thermal cascade and yielding the targeted bifunctional γ-allenyl alkylidenemalononitriles. Considering that the allene is delivered axially and that the axial allene is *preferred* over the equatorial allene, we reasoned that biasing one chair conformation over another could halt the thermal cascade following allene formation.

Scheme 4. Preventing thermal cascade by substructure bias



We prepared substrates **1e, 1h – 1i**, which would *lock* the allene in a non-acidic conformation, and substrates **1j – 1m**, which would *bias* the allene in a non-acidic conformation (Scheme 4). The locked substrates underwent smooth transformation and gave high yields of the desired allenes **2e, 2h,** and **2i**. Notably, this transformation was tolerant to alkyne substitution, which was not possible in the simple system (e.g. **1c**). A large ^{t}butyl group also gave a high yield of the desired allene **2j** when the starting enyne was terminal. The analogous internal enyne **1k** (R = Me) also yielded the desired allene **2k**. Although modest yield and conversion was observed, this is a substantial improvement, as **1c**, lacking the biasing group, shows no allene product. Similarly, the menthone derived enynes successfully yielded allenes **2i** and **2m.** In this case, smaller alkyl groups on the cyclohexyl ring, when compounded, are effective at biasing chair conformations.

THE REDUCTIVE ENYNE COPE REARRANGEMENT

In the above section, we described that the thermal cascade can be halted at the allene stage when utilizing substrates that prefer one chair conformation over the other (locked or biased substrates). Although pleased to better understand the Cope rearrangement and yield structurally unique allenes, this approach is somewhat limiting, as it requires specific biasing elements. A method not tied to a structural architecture would yield a wider scope. We hypothesized that the Cope rearrangement in the presence of a reductant that could chemoselectively react with the *in situ* generated alkylidenemalononitrile-moiety would divert the transformation before the γ-allenylalkylidenemalononitrile can further isomerize (Scheme 5). If achieved, this would yield bifunctional allenyl malononitriles H_2-**2**, useful building blocks for synthesis.

Scheme 5. The Reductive Enyne Cope Rearrangement

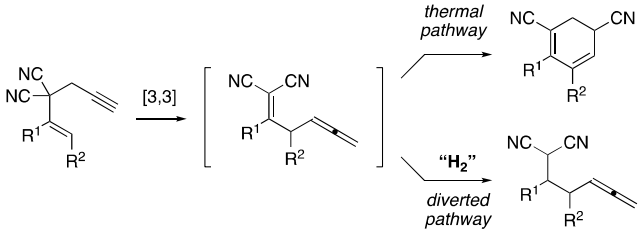
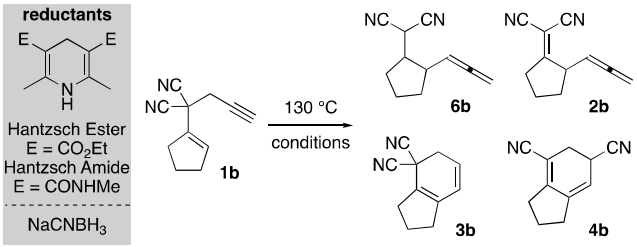


Table 1. Development of the reductive Cope rearrangement



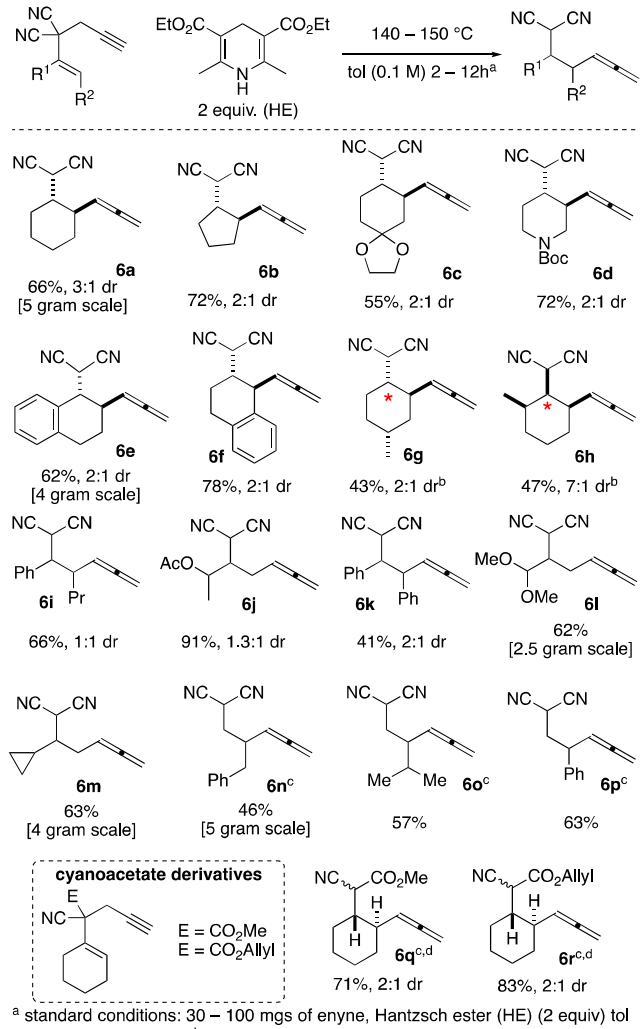
entry	Reductant (2 equiv.)	Solvent	(h)	% conv.	6b	2b	3b	4b
1	Hantzsch Ester	tol	2	40	1	0	0	0
2	Hantzsch Ester	tol	7	>95	1 (70%)	0	0	0
3	Hantzsch Ester	propanol	2	35	1	0	0	0
4	Hantzsch Ester	tol:PrOH (5:1)	2	52	1	0	0	0
5	Hantzsch Ester	tol:TFE (5:1)	2	64	3	0	0	1
6	Hantzch Amide	tol	2	39	0	0	1	0
7	$NaCNBH_3$	tol	2	40	0	0	1	1

To test the hypothesis, we prepared the 3,3-dicyano-1,5-enyne **1b** derived from cyclopentanone, malononitrile, and propargyl bromide and began examining the reductive enyne Cope rearrangement (Table 1). After some experimentation, it was found that adding Hantzsch ester (HE) to the reaction results in product **6b** exclusively in good yield as a mixture of diastereomers (entry 1).[8] Other solvents and mixtures of solvents provided the desired product with varying efficiency. We also explored a few other reductants that were unsuccessful.

With optimized conditions in hand, we found that many allenyl malononitriles could be prepared (Scheme 6). The scope was broad, in part, due to the ready availability of the 1,5-enynes examined. For example, products **6a – 6h** were prepared from malononitrile, propargyl bromide and a variable cycloalkanone: cyclohexa-

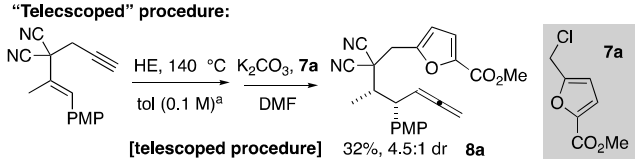
none (**6a**), cyclopentanone (**6b**), protected 1,4-cycloalkandione (**6c**), N-Boc piperidinone (**6d**), α-tetralone (**6e**), β-tetralone (**6f**), 4-methylcyclohexanone (**6g**), and 2-methylcyclohexanone (**6h**). We also examined acyclic ketones (**6i – 6m**) and aldehydes (**6n – 6p**). The reaction is generally tolerant to functional groups such as ketals (**6c**), acetals (**6l**), Boc-protected amines (**6d**), esters (**6j**), and cyclopropanes (**6m**). Regarding diastereoselectivity, the reduction step is poorly selective, generally speaking. However, the Cope rearrangement-step is diastereoselective (**6g** and **6h**). In both these cases, the reduction step still yields a diastereomeric mixture. Products **6a**, **6e**, **6l**, **6m**, and **6n** were prepared on the > gram scale. Generally speaking, the standard scale (50 – 100 mgs) and the scale up procedures (2 – 5 grams) gave similar results.

Scheme 6. Scope of the reductive Cope rearrangement.



[a] standard conditions: 30 – 100 mgs of enyne, Hantzsch ester (HE) (2 equiv) tol (0.1 M), 130 – 180 °C [b] the minor product is epimeric at the starred position [c] 180 °C *in lieu* of 140 – 150 °C [d] 4 equiv. HE

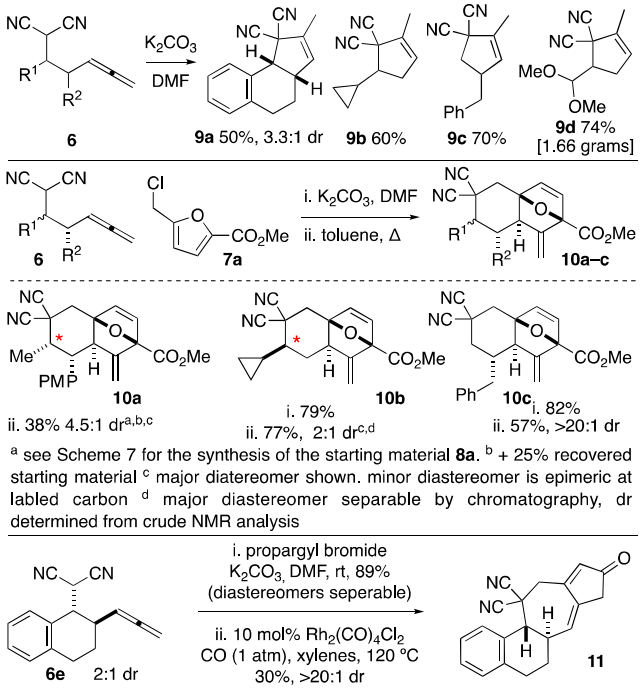
"Telescoped" procedure:



In final examples related to the scope of the reductive enyne Cope rearrangement, methyl and allyl cyanoacetate derived substrates were examined (Scheme 6). Although they required a higher temperature to react (180 °C *in lieu* of 140 – 150 °C), they still yielded the desired allenes **6q** and **6r** in good yield with the expected modest diastereoselectivity.

In a few cases, we found that the reductive Cope product was inseparable from the Hantzsch ester. We found that "telescoping" the reaction by malononitrile alkylation with **7a** would allow for isolation of target building blocks, in this case the furan-allene building block **8a** (Scheme 6).

Scheme 7. Utility of allenyl malononitrile building blocks



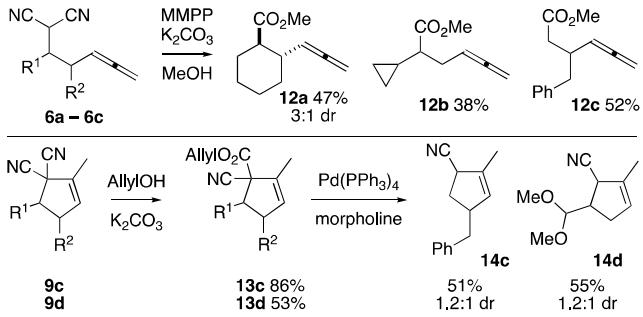
[a] see Scheme 7 for the synthesis of the starting material **8a**. [b] + 25% recovered starting material [c] major diatereomer shown. minor diastereomer is epimeric at labled carbon [d] major diastereomer separable by chromatography, dr determined from crude NMR analysis

We next examined the utility of the allene/malononitrile building blocks (Scheme 7). Functionally dense methylcyclopentenes **9** can be prepared by a base-catalyzed cycloisomerization.[11] Decalin ring systems **10** are accessible by an alkylation (with **7a**)/thermal [4+2] strategy.[9] Hydroazulenes **11** are prepared by allenic-Pauson-Khand reaction (PKR) under the conditions reported by Brummond.[8]

As final experiments, we explored how the malononitrile moiety can be manipulated (Scheme 8). Monoalkylmalononitriles can be thought of as carboxylate equivalents: Using magnesium monoperoxyphthalate (MMPP) as an oxidant in methanol, allene/carboxylic esters **12** are prepared.[10] In the cases of disubstituted malononitriles, formal decyanation can mildly be achieved by Pinner reaction with allyl alcohol to the allyl cyanoacetates **13** followed by Pd-catalyzed decarboxylative protonation yielding mono-nitriles **14**.[12]

In conclusion, we have explored various aspects of the rearrangement of 3,3-dicyano-1,5-enynes. Through experimental and computational studies, we have a better understanding of how to control and halt the rearrangement at the prior to allene isomerization, as well as a method to divert from the thermal pathway by chemoselective reduction. The bifunctional allenyl alkylidenemalononitriles and allenyl malononitriles are also well suited for manipulation into a variety of cyclic or acyclic building blocks. Future directions include complex molecule synthesis, scope expansion, improving the diastereoselectivity, and identifying enantioselective variants.

Scheme 8. Malononitrile functional group interconversions.



ASSOCIATED CONTENT

Supporting Information

- The Supporting Information is available free of charge on the ACS Publications website.
- Experimental procedures
- Compound characterization (^{1}H NMR, ^{13}C NMR, and HRMS)
- ^{1}H and ^{13}C NMR reprints

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Graphical Abstract Figure: