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Promoting Thermodynamically Unfavorable [3,3] Rearrangements by Chemoselective Reduction

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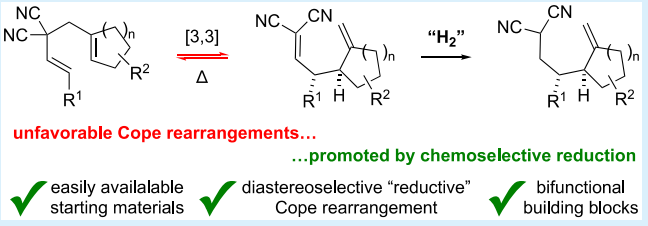
Supporting Information

ABSTRACT: Herein described is a strategy for promoting thermodynamically unfavorable [3,3] Cope rearrangements. 3,3-Dicyano-1,5-dienes that are resistant to the thermal rearrangement can be promoted under reductive conditions. The reduced Cope products are versatile, bifunctional building blocks.



The original Cope rearrangement[1−3] substrates, 3,3-dicyano-1,5-dienes **1**, are attractive building blocks for chemical synthesis. They are prepared from ketones/aldehydes, malononitrile, and an allylic electrophile by Knoevenagel condensation[4] then deconjugative alkylation,[5−11] and are thermally reacted to form γ-allylalkylidenemalononitriles **2** at temperatures ranging from room-temperature to 150 °C.[1−3,7,9,11−17] Furthermore, Cope products can be converted into diverse scaffolds in rapid fashion; e.g., densely functionalized cycloheptenes[12,13,15−17] and linear carboxylate derivatives.[18−25]

Although numerous 3,3-dicyano-1,5-dienes are reported to undergo high conversion [3,3] rearrangements (high thermodynamic favorability), we have realized several 1,5-diene substitution patterns that result in an equilibrium not favoring the desired product side.[16,26] For example, 3,3-dicyano-1,5-dienes **I** and **II** derived from malononitrile and cyclic-allylic electrophiles or cinnamyl electrophiles, respectively, are not thermodynamically favored to progress (Figure 1).[26] It is suspected that the synthesis of torsionally strained 3°/3°-C−C bonds and decreased olefin hyperconjugation or styrene deconjugation can be contributing factors to the apparent increased ground-state energies of the desired γ-allylalkylidenemalononitriles.

To increase the general applicability of the original Cope rearrangement, thermodynamic limitations need to be addressed. In this regard, it is hypothesized that under Cope rearrangement-equilibrium conditions, a nucleophilic reductant can selectively react at the minor side of the equilibrium by conjugate reduction: the equilibrium is constantly re-established upon transformation to reduced Cope products (H_2-**2**) (Le Chatelier's principle; Scheme 2). The reduced Cope products would have similar value to the thermal products as they are bifunctional (malononitrile and alkene functional handles) and can be utilized in similar fashion to that described in Scheme 1. Similarly, we recently reported that reductive Cope transformations could divert the thermal cascade of 3,3-dicyano-1,5-enynes to yield allenylmalononitriles over the known benzenoid products.[12] To reiterate and

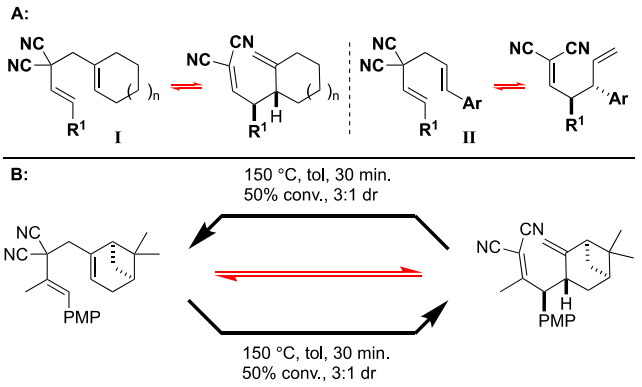
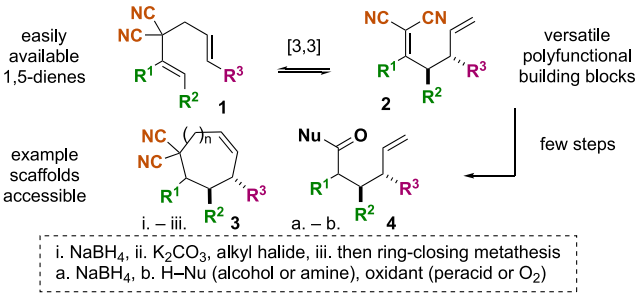


Figure 1. (A) Examples of 3,3-dicyano-1,5-dienes that do not efficiently rearrange to their respective γ-allylalkylidenemalononitriles. (B) Example case where either side of the equilibrium can be isolated and thermodynamically equilibrated.

Scheme 1. Original Cope Rearrangement and Examples of How To Utilize These Substrates in Synthesis



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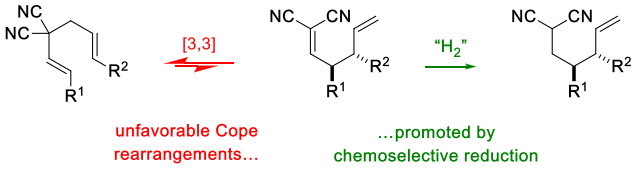
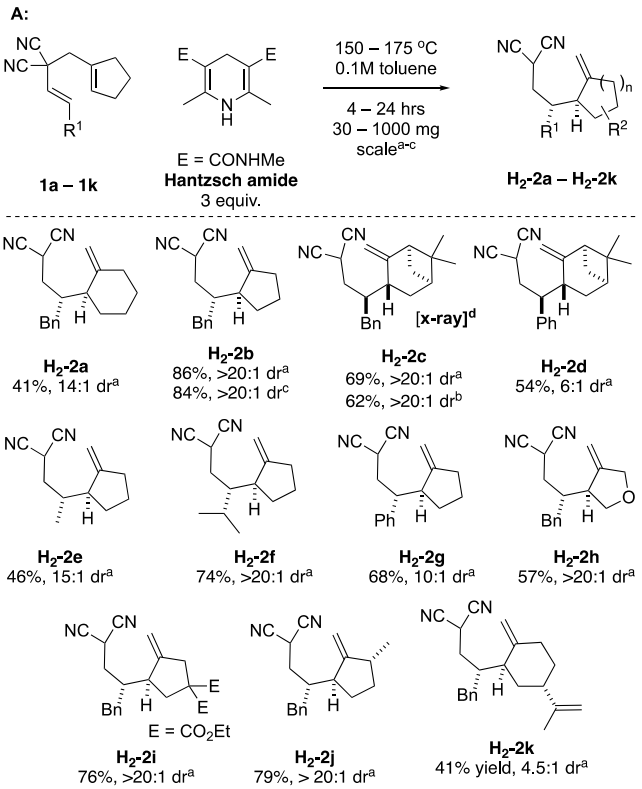
Scheme 2. Reductive Cope Rearrangement Can Promote Unfavorable Cope Rearrangements by Harnessing Le Chatelier's Principle



compare, the enynes are favored to progress to benzenoid products, whereas many dienes are not.[26] Herein, we report successful implementation of this hypothesis and representative examples of how the reductive Cope products can be utilized in chemical synthesis.

After extensive experimentation with different conditions and reductants, it was found that 100% conversion of 1,5-diene **1a**−**1k** to reduced Cope products H_2-**2a**−H_2-**2k** could be achieved using Hantzsch amide in toluene, at 150−175 °C in crimped pressure vials (small scale) or screw cap heavy-walled round-bottom flasks (larger scale) (Scheme 3).[27−29] We opted to use Hantzsch amide[27] over the commercially available Hantzsch ester due to challenges with purification: the Hantzsch pyridine byproduct is water-soluble. The reaction proceeded smoothly with a variety of "R1" groups, which are derived from an aldehyde feedstock. The cyclic allylic reagent could be cyclohexenyl (**2a**), cyclopentenyl (**2b, 2e**−**2g**), or contain functional groups such as an ether (**2h**) or a malonate (**2i**). We also explored a variety of chiral substrates where the stereocenter is found within the carbocycle (myrtenol- (**2c**−**2d**), perillaldehyde- (**2k**), and citronellal-derived (**2j**)). In general, the Cope rearrangements of this type were diastereoselective, and the reduction step occurred faster than epimerization, which was observed under thermal conditions (Figure 1). Another notable result was the isolation of product H_2-**2d**. This particular substrate showed little sign of thermal Cope rearrangement by ^{1}H NMR analysis (<5% conversion by NMR). Thus, even highly unfavorable Cope rearrangements can proceed with added reductant.

Scheme 3. Reductive Cope Rearrangement of 3,3-Dicyano-1,5-dienes Derived from Cyclic-allylic Electrophiles, Aldehydes, and Malononitrile

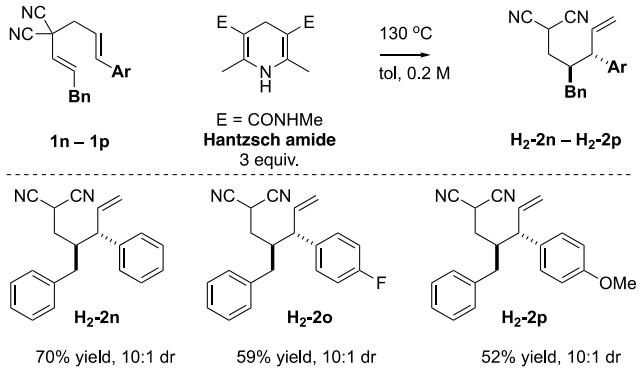


[a] 30 – 100 mg, [b] 500 mg scale, [c] 1 gram scale [d] a X-ray of a derivative of this molecule was obtained to confirm diastereoselectivity. See the supporting information.

In its current form, the malononitrile group is significant. It was found that cyanoacetate- and malonate-derived 1,5-dienes **1l** and **1m**, respectively, do not react under the conditions optimized for the 3,3-dicyano-1,5-dienes (Scheme 3B). A similar observation was made by Cope in his seminal work: malononitrile 1,5-dienes are more reactive than their cyanoacetate and malonate counterparts.[1−3]

We next examined reductive Cope rearrangements for achieving styrene deconjugation (Scheme 4).[13,16] Under similar conditions, we were able to styrene-deconjugate phenyl (H_2-**2n**), electron-deficient (H_2-**2o**), and electron-rich (H_2-**2p**) styrene-containing substrates to yield bifunctional alkenylmalononitriles bearing a 1,3-diaryl motif. Our previous solution to this problem was to utilize [3,3] "promoting-groups".[13]

Scheme 4. Reductive Cope Rearrangement of 3,3-Dicyano-1,5-dienes Derived from Cinnamyl Electrophiles, Aldehydes, and Malononitrile



The potential utility of the reductive Cope products was also explored (Scheme 5). By malononitrile allylation and ring-closing metathesis (RCM), 5−7 (hydroazulenes) and 6−7 scaffolds of **3** can be accessed (Scheme 5A).[30] Monoalkylmalononitriles can also be converted readily to esters by oxidative esterification.[18−25] For example, the reduced Cope product H_2-**2b** was converted to the exomethylenecyclopentane-ester building block **4a** when magnesium monoperoxyphthalate (MMPP) was utilized as an oxidant in methanol.[24] Such scaffolds may find value in hydrindane synthesis (e.g., **5**) by a Prins-like cyclization (Scheme 5B).[31,32] A few other exomethylenecycloalkane-ester building blocks **4b**−**4d** were prepared by oxidative decyanation in modest to excellent yields. Finally, oxidative amidation can be utilized to directly convert the malononitrile to amides (Scheme 5C).[21] In this

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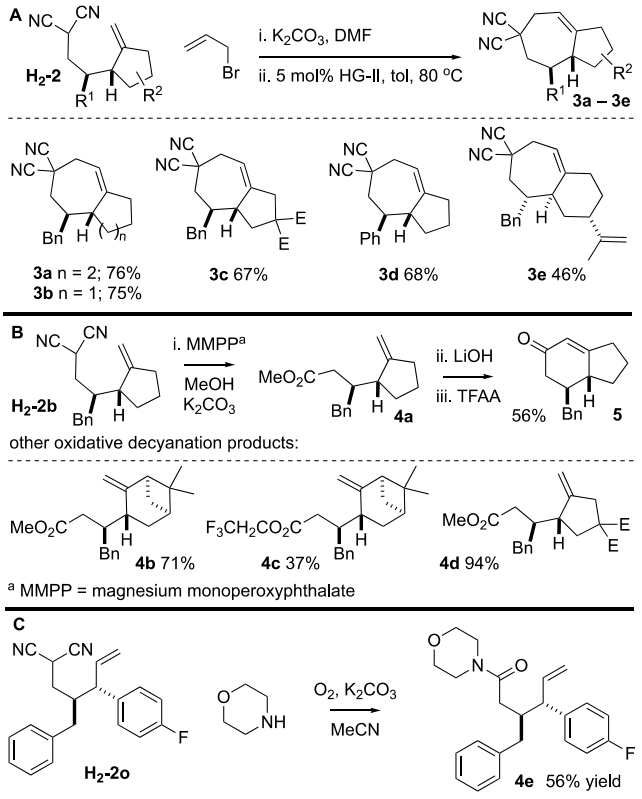
Scheme 5. Reductive Cope Products Are Versatile Building Blocks



case, a complex, drug-like 1,3-diarylcarboxylic amide **4e** was prepared.

In conclusion, we have devised a strategy for promoting thermodynamically unfavorable Cope rearrangements of 3,3-dicyano-1,5-dienes whereby a chemoselective reduction allows for complete conversion. Under equilibrium conditions, the "minor" but desired side of the equilibrium bears an activated olefin that can be chemoselectively reduced by Hantzsch amide. Essentially, Le Chatelier's principle is harnessed to yield valuable reduced Cope products. We envisage that the chemical space accessible by this transformation will find value in complex, drug-like molecule synthesis. Finally, this general principle is likely accessible to other unfavorable Cope rearrangements, which will be explored in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02057.

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

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Notes

The authors declare no competing financial interest.

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