Construction of vicinal 4°/3°-carbons *via* reductive Cope rearrangement.

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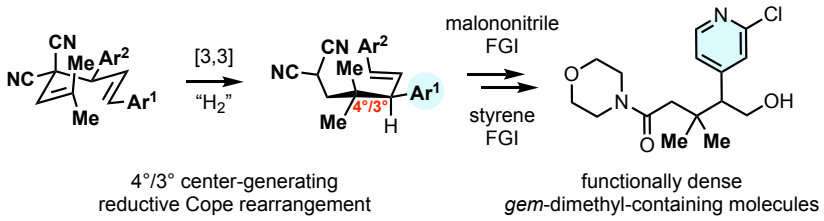
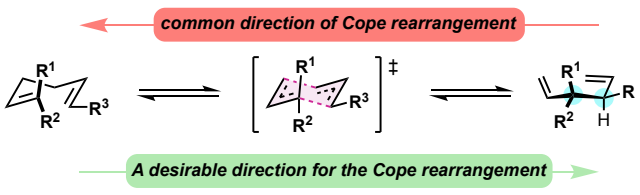
Abstract: Herein reported is a strategy for constructing vicinal 4°/3° carbons *via* reductive Cope rearrangement. Substrates have been designed which exhibit Cope rearrangement kinetic barriers in the range of ~23 kcal/mol with isoenergtic favorability (ΔG ~0). These fluxional/shape-shifting molecules can be *driven forward* by chemoselective reduction to useful polyfunctionalized building blocks.



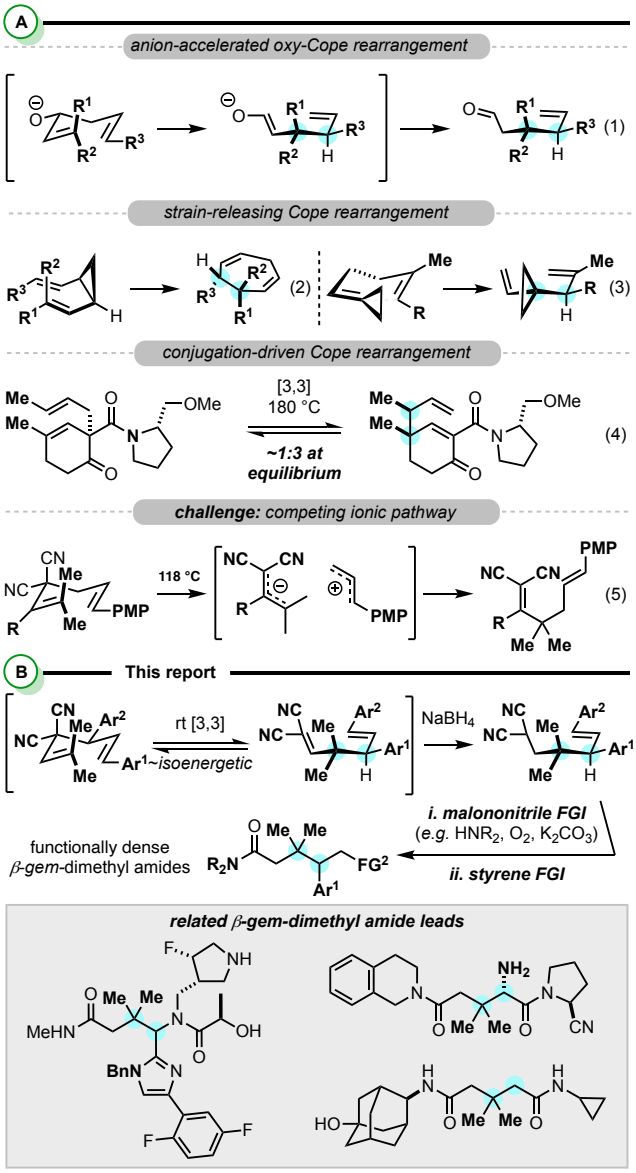
Constructing sterically congested vicinal quaternary–tertiary carbons (4°/3° carbons) *via* Cope rearrangement is currently quite limited with only a handful of papers on the subject published over the past 40 years. This stands in stark contrast to the plethora of other methods for establishing sterically congested vicinal carbons.[1-5] Central to the challenge are kinetic and thermodynamic issues associated with the transformation. In the simplest sense, Cope rearrangements proceed in the direction that results in highest alkene substitution (Figure 1).[6,7] To forge 4°/3° motifs by Cope rearrangement, additional driving forces must be introduced to *reverse* the [3,3] directionality and compensate for the energetic penalty associated with the steric and torsional strain of the targeted vicinal 4°/3° motif. With limited reports in all cases, *oxy*-Cope substrates (Scheme 1, equation 1),[8-14] divinylcyclopropanes (Scheme 1, equation 2),[15-20] and vinylidenecyclopropane-based 1,5-dienes[21] (Scheme 1, equation 3) have demonstrated favorability for constructing vicinal 4°/3° carbons. Malachowski *et al* put forth a series of studies on the construction of quaternary centers *via* Cope rearrangement driven forward by a conjugation event (Scheme 1, equation

Figure 1: *Cope equilibrium of 1,1,6-trisubstituted 1,5-dienes*



4).[22–25] In their work, a single example related to the construction of vicinal 4°/3° centers was disclosed, though kinetic (180 °C) and thermodynamic (equilibrium mixtures) challenges are also observed.[23] And of particular relevance to this work, Wigfield *et al.* demonstrated that 3,3-dicyano-1,5-dienes with the *potential* to generate vicinal 4°/3° carbons instead react *via* an ionic mechanism yielding the *less congested* products (Scheme 1, equation 5).[26]

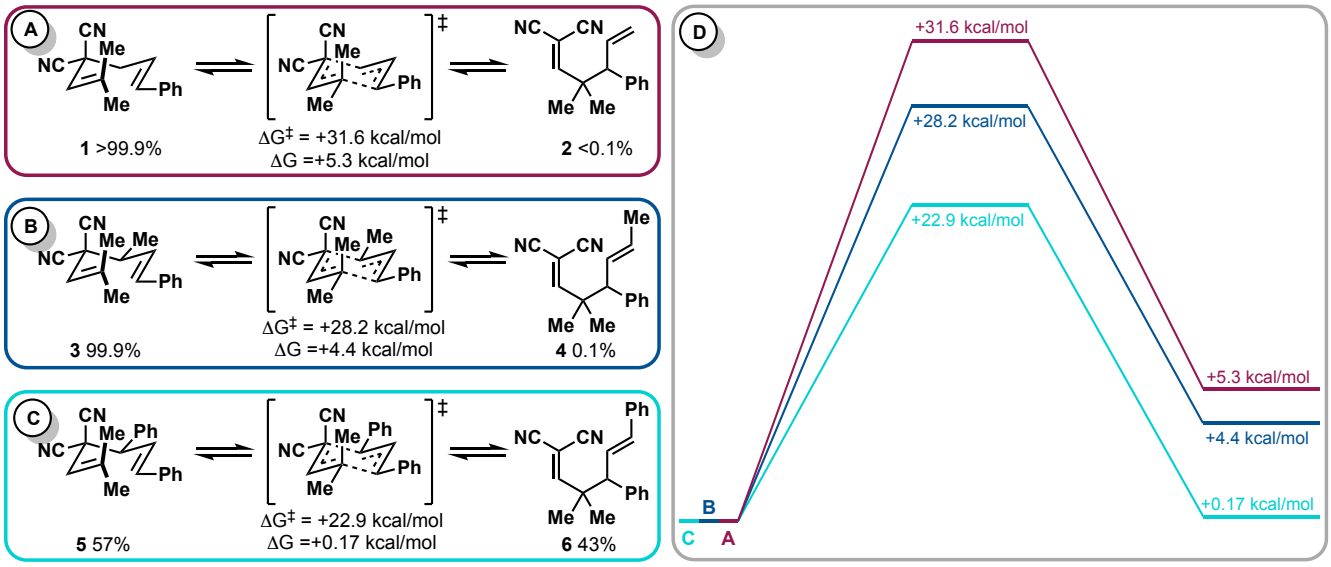
Scheme 1: ***A:*** *Cope rearrangements for constructing vicinal 4°/3°-center* ***B:*** *This report.*



Our group has been examining strategies to decrease kinetic barriers and increase the thermodynamic favorability of 3,3-dicyano-1,5-diene-based Cope substrates.[27–31] Beyond the simplest, unsubstituted variants, this class of 1,5-diene is not particularly reactive in both a kinetic and thermodynamic sense (e.g. Scheme 1, equation 5).[26,32] Reactivity issues aside, these substrates are attractive building blocks for two main reasons: (1) they have straightforward accessibility from alkylidenemalononitriles and allylic electrophiles by deconjugative allylic alkylation.[33] (2) The 1,5-diene *termini* are substantially different (malononitrile vs simple alkene) thus allowing for orthogonal functional group interconversion facilitating target and analog synthesis.[34] Herein we report that a combination of 1,5-diene *structural engineering*[31,35] and *reductive conditions* (the reductive Cope rearrangement[29,30]) can result in the synthesis of building blocks containing vicinal *gem*-dimethyl 4°/3° carbons along with orthogonal malononitrile and styrene functional groups for interconversion (Scheme 1B). On this line, malononitrile can be directly converted to amides[34] yielding functionally dense β-*gem*-dimethylamides, important pharmaceutical scaffolds.[36]

This project began during the Covid-19 pandemic *lockdown* (ca. March – May 2020). As such, we were not permitted to use our laboratory out of an abundance of caution. We took this opportunity to first

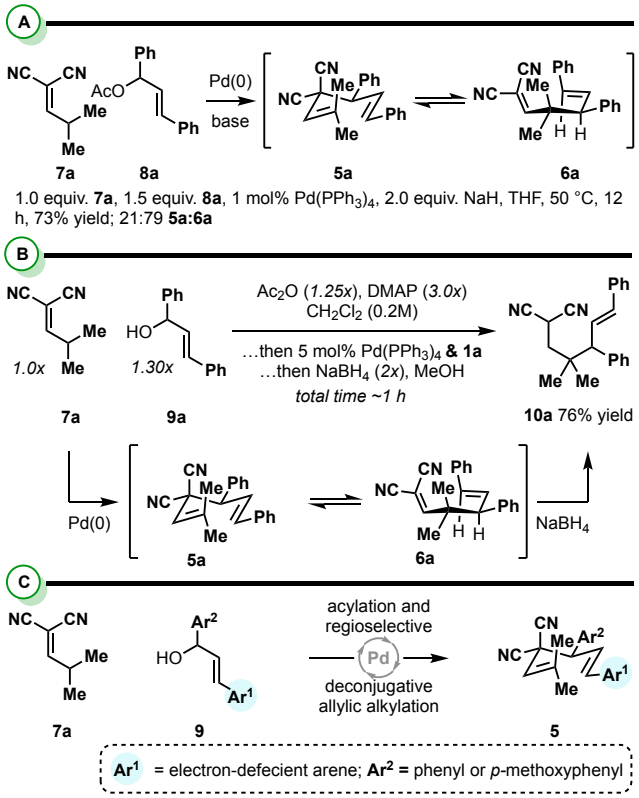
Scheme 2: *Computational analysis of 3,3-dicyano-1,5-diene that in theory could result in vicinal 4°/3° carbons.* ***A:*** *4-unsubstituted 3,3-dicyano-1,5-diene.* ***B:*** *4-methyl 3,3-dicyano-1,5-diene.* ***C:*** *4-phenyl 3,3-dicyano-1,5-diene.* ***D:*** *visualization of the kinetic- and thermodynamic differences of transformations* ***A – C****.*



computationally investigate a Cope rearrangement that could result in vicinal 4°/3° carbons (Scheme 2). Then, when permitted to safely return to the lab, we would experimentally validate our findings (*vide infra*). From our previous work, it is known that by adding either a 4-aromatic group[28] or a 4-methyl group[31] to a 3,3-dicyano-1,5-diene, low barrier (rt – 80 °C) diastereoselective Cope rearrangements can occur. Notably, the 4-substituent was found to *destabilize the starting material* (weaken the C3–C4 bond, conformationally bias the substrate for [3,3]), and stabilize the product side of the equilibrium via resonance (phenyl group) or hyperconjugation (methyl group). In this study, we modeled substrates **1, 3,** and **5** that have variable 4-substitution and would result in vicinal *gem*-dimethyl- and phenyl- containing 4°/3° carbons upon Cope rearrangement to **2, 4**, or **6**, respectively. We chose to target this motif due to likely synthetic accessibility from simple starting materials but also because of the important and profound impact that *gem*-dimethyl groups impart on pharmaceuticals.[36] Substrate **1** lacking 4-substitution had an extremely unfavorable kinetic and thermodynamic profile ($\Delta G^{\ddagger}$ = 31.6; ΔG = +5.3 kcal/mol). When a 4-methyl group was added, the kinetic barrier ($\Delta G^{\ddagger}$) dropped appreciably to 28.2 kcal/mol; however, the thermodynamics were still highly unfavorable (ΔG = +4.4 kcal/mol). Most excitingly, it was uncovered that the 4-phenyl group dramatically impacted the kinetics and thermodynamics: the [3,3] has a barrier of 22.9 kcal/mol ($\Delta G^{\ddagger}$) and is ~isoenergetic (ΔG = +0.17 kcal/mol). Thus, the reaction appears to be fluxional/shape-shifting at room temperature.[37–41]

The class of substrate uncovered from our computational investigation could be accessed from γ,γ-dimethyl-alkylidenemalononitrile (**7a**) and 1,3-diarylallyl electrophiles (such as **8a**) by Pd-catalyzed deconjugative allylic

Scheme 3: ***A:*** *Observation of fluxional [3,3].* ***B:*** *Optimization of a reductive Cope rearrangement protocol for constructing vicinal 4°/3° centers.* ***C:*** *The Pd-catalyzed deconjugative allylic alkylation must be regioselective.*

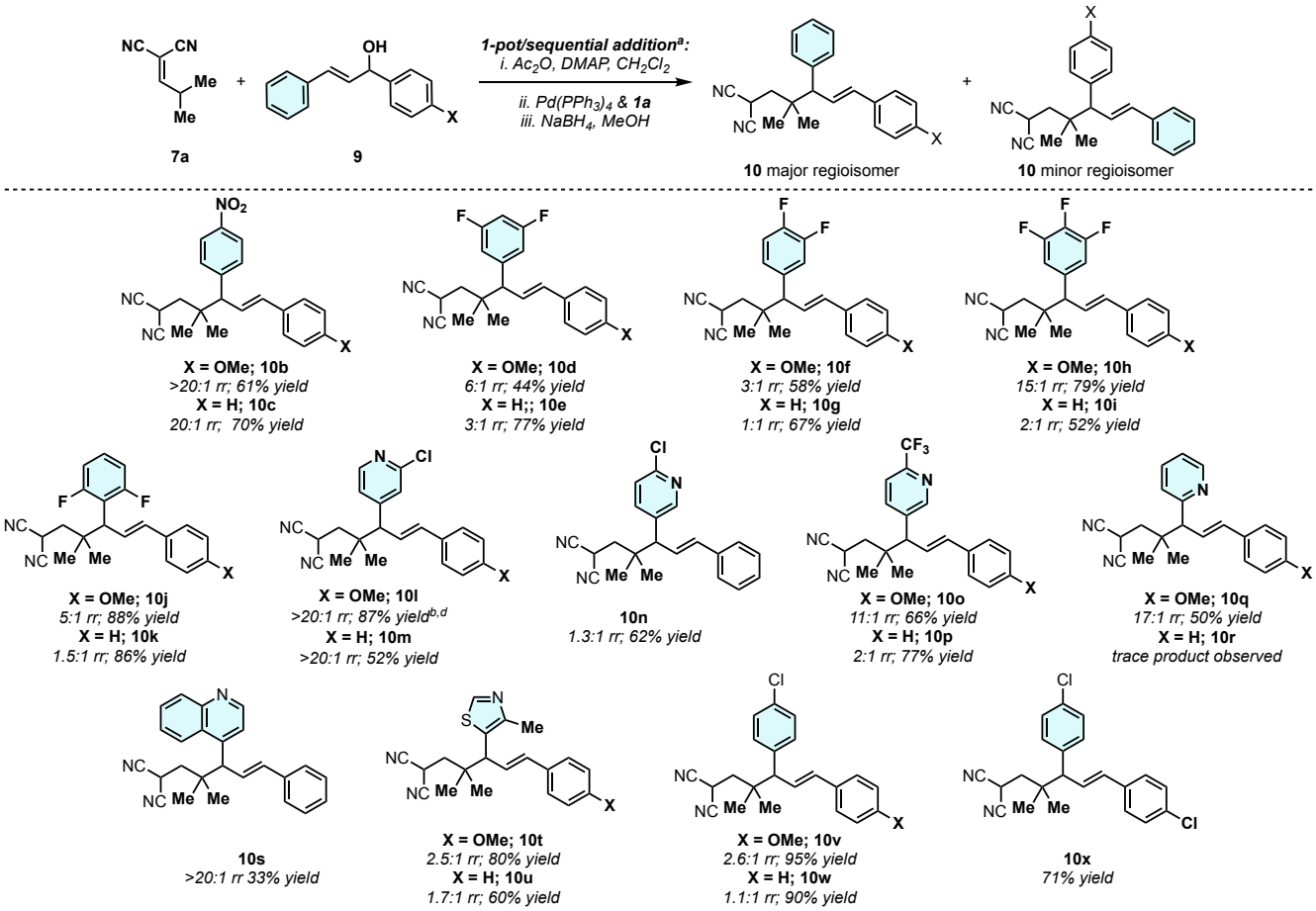


alkylation (Scheme 3A).[33] As such, model 1,5-diene **5a** was prepared to verify the computational results. It was found that upon synthesis of **5a**, an inseparable 21:79 mixture of 1,5-diene **5a** and the 1,5-diene **6a** was observed. The predicted ratio of **5a** to **6a** was 57:43 (Scheme 2C). These two results are within the error of the calculations (*predicted;* slightly endergonic. observed; slightly exergonic).

With respect to the synthetic methodology, we aimed to increase the overall efficiency of the sequence (Scheme 3B). It was found that the direct coupling of **7a** with diphenylallyl alcohol **9a** could take place in the presence of DMAP, Ac_2O, and $Pd(PPh_3)_4$. When the coupling was complete, methanol and $NaBH_4$ were added to drive the Cope equilibrium forward, yielding the reduced Cope rearrangement product **10a** in 75% isolated yield. Notably, **5a**, which cannot react with $NaBH_4$ under these conditions, is not observed. This is further evidence that the Cope equilibrium is driven forward by the reduction and that the [3,3] equilibrium is fluxional at room temperature. In terms of practicality and efficiency, this method utilizes diphenylallyl alcohols, which are more stable and synthetically accessible than their respective acetates, and the [3,3] equilibrium mixture can be directly converted dynamically to a single reduced product.

With an efficient protocol in hand for constructing malononitrile–styrene-tethered building blocks featuring central vicinal 4°/3° carbons, we next examined the scope of the transformation (Scheme 4). We chose diarylallyl alcohols with the propensity to react regioselectively *via* an electronic bias (Scheme 3C).[42,43] The combination of *p*-nitrophenyl and phenyl (**10b**) or *p*-methoxyphenyl (**10c**) yielded regioselective outcomes with the electron-deficient arene at the allylic position. This is consistent with the expected regiochemical outcome where the nucleophile reacts preferentially at the α-position and the electrophile reacts at the allylic position bearing the donor-arene (Scheme 3C).[42,43] Then, reductive Cope rearrangement occurs to position the electron-deficient arene adjacent to the *gem*-dimethyl quaternary center. This is an exciting outcome as many

Scheme 4: *Scope of the 4°/3°-center-generating reductive Cope rearrangement.*

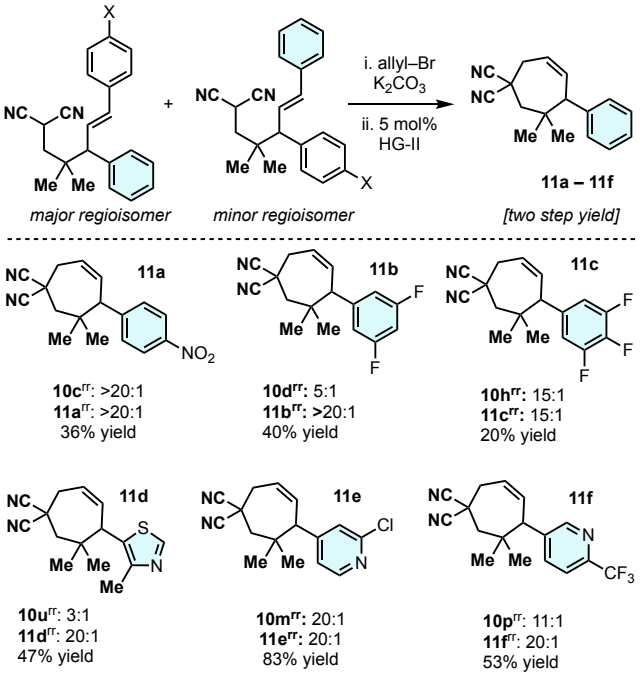


pharmaceutically relevant hetero(arenes) are electron deficient. Thus, fluorinated arenes were installed at the allylic position of products **10d – 10k**. While the phenyl group resulted in poor regioselectivity (1:1 – 3:1), the *p*-methoxyphenyl group enhanced the regiomeric ratios in all cases (3:1 – 15:1). The degree of selectivity is correlated with the number and position of fluorine atoms. *N*-Heterocycles could be incorporated with excellent regioselectivity, generally speaking (**10l – 10q**). For example, 3-chloro-4-pyridyl (**10l/10m**) groups were installed at the allylic position with >20:1 rr. 4-Chloro-3-pyridyl was poorly regioselective (**10n**), but the combination of 4-trifluomethyl-3-pyridyl/*p*-methoxyphenyl (**10o**) gave good regioselectivity of 11:1. 2-Pyridyl/*p*-methoxyphenyl (**10q**) was also a regioselective combination. We also examined a few other heterocycles including quinoline (**10s**) and thiazole (**10t** and **10u**) with excellent and modest regioselectivity observed, respectively. As a general trend, when the arenes on the allylic electrophile become *less polarized*, poor regioselectivity is observed in the Pd-catalyzed allylic alkylation. For example, the combination of *p*-chlorophenyl and *p*-methoxyphenyl (**10v**) or phenyl (**10w**) yields regioisomeric mixtures of products. This can be circumvented by utilizing symmetric electrophiles (to **10x**).

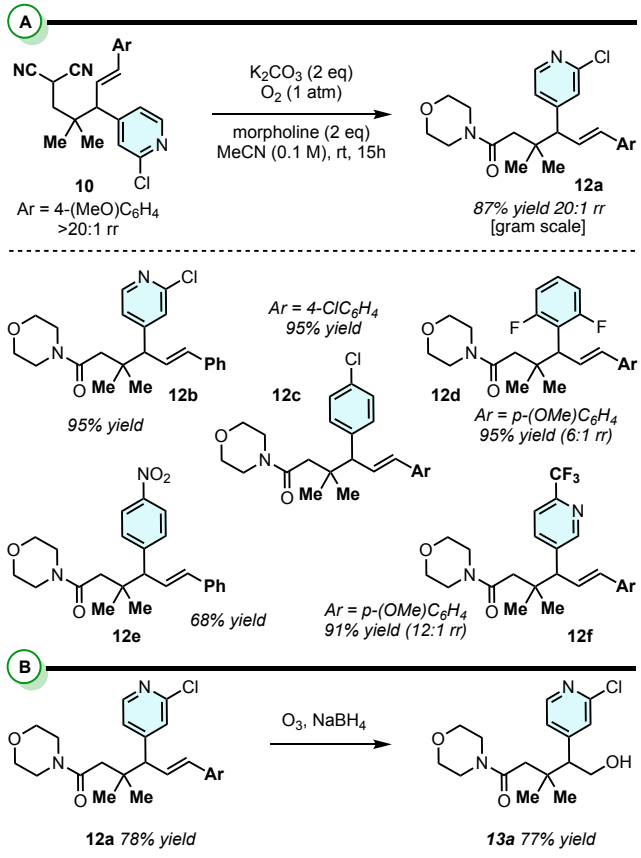
The phenyl or the *p*-methoxyphenyl group is necessary to achieve the 4°/3° carbon-generating Cope rearrangement: it functions as an "activator" by lowering the kinetic barrier and increasing thermodynamic favorability. These activating groups can be removed through alkene C=C cleavage reactions (e.g. metathesis (Scheme 5) and ozonolysis (Scheme 6B)). In this regard, highly substituted cycloheptenes **11** were prepared by allylation and metathesis (Scheme 4).[28,44,45] The yields were modest to excellent over this two-step sequence. In many cases, where **10** exists as a mixture of regioisomers, the major allylation/RCM products **11** could be chromatographically separated from their minor constituents. As shown in Scheme 6A, the malononitrile can be transformed *via* oxidative amidation[34] to products **12** containing a dense array of pharmaceutically relevant functionalities (amides, *gem*-dimethyl, fluoroaromatics, and heteroaromatics). Following this transformation, ozonolysis terminated with a $NaBH_4$ quench installs an alcohol moiety on small molecule **13a**.

In conclusion, we have developed a method to construct *vicinal gem*-dimethyl 4°/3° carbons *via* reductive Cope rearrangement. 1,5-diene substrates bearing a key 4-phenyl or *p*-methoxyphenyl group have low kinetic barriers for Cope rearrangement. The 1,5-dienes are fluxional/shape-shifting ($\Delta G^{\ddagger}$ ~ 23 kcal/mol, ΔG ~0 kcal/mol) and reductive conditions are utilized to drive the rearrangement forward, toward products

Scheme 5: *Removal of the "activating group" by ring-closing metathesis.*



Scheme 6: ***A:*** *oxidative amidation of malononitrile.* ***B:*** *Removal of "activating group" by ozonolysis.*



containing a central *gem*-dimethyl/arene motif flanked on either side by a malononitrile and styrene moiety, respectively. These functional groups can be manipulated to construct unique molecular architectures such as cycloheptenes (Scheme 5) and amides (Scheme 6). Future directions involve expanding the scope of this transformation, developing enantioselective variants, and identifying specific opportunities for molecular synthesis and lead generation in medicinal chemistry campaigns.

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