# Chemical Science

# EDGE ARTICLE



Cite this: Chem. Sci., 2022, 13, 1951

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 15th November 2021 Accepted 20th January 2022

DOI: 10.1039/d1sc06307c

rsc.li/chemical-science

# Construction of vicinal 4°/3°-carbons via reductive Cope rearrangement<sup>+</sup>

Kristin M. Sobie, Matthew Albritton, Yinuo Yang, Mariana M. Alves, Adrian Roitberg\* and Alexander J. Grenning \*

Herein reported is a strategy for constructing vicinal  $4^{\circ}/3^{\circ}$  carbons *via* reductive Cope rearrangement. Substrates have been designed which exhibit Cope rearrangement kinetic barriers of ~23 kcal mol<sup>-1</sup> with isoenergetic favorability ( $\Delta G \sim 0$ ). These fluxional/shape-shifting molecules can be driven forward by chemoselective reduction to useful polyfunctionalized building blocks.

Constructing sterically congested vicinal quaternary-tertiary carbons  $(4^{\circ}/3^{\circ} \text{ carbons})$  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.<sup>1-5</sup> 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 (Fig. 1).<sup>6,7</sup> 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  $4^{\circ}/3^{\circ}$  motif. With limited reports in all cases, oxy-Cope substrates (Scheme 1, eqn (1),<sup>8-14</sup> divinylcyclopropanes (Scheme 1, eqn (2)),<sup>15-20</sup> and vinylidenecyclopropane-based 1,5-dienes<sup>21</sup> (Scheme 1, eqn (3)) have demonstrated favourability 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, eqn (4)).<sup>22-25</sup> 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  $4^{\circ}/3^{\circ}$  carbons instead react via an ionic mechanism yielding the less congested products (Scheme 1, eqn (5)).26

Our group has been examining strategies to decrease kinetic barriers and increase the thermodynamic favourability of 3,3dicyano-1,5-diene-based Cope substrates.<sup>27-31</sup> 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, eqn (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 analogue synthesis.34 Herein we report that a combination of 1,5-diene structural engineering<sup>28,31</sup> and reductive conditions (the reductive Cope rearrangement<sup>29,30</sup>) 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<sup>34</sup> yielding functionally dense β-gem-dimethylamides, important pharmaceutical scaffolds.35

ROYAL SOCIETY OF **CHEMISTRY** 

View Article Online

View Journal | View Issue

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 computationally investigate a Cope rearrangement that could result in vicinal  $4^{\circ}/3^{\circ}$  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<sup>28</sup> or a 4-methyl group<sup>31</sup> 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



Fig. 1 Cope equilibrium of 1,1,6-trisubstituted 1,5-dienes.

Department of Chemistry, University of Florida, PO Box 117200, Gainesville, FL 32611, USA. E-mail: grenning@ufl.edu; roitberg@ufl.edu

<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Experimental details, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS data and reprints. See DOI: 10.1039/d1sc06307c



Scheme 1 (A) Cope rearrangements for constructing vicinal  $4^\circ/3^\circ$  - centers (B) this report.

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 modelled 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.35 Substrate 1 lacking 4-substitution had an extremely unfavourable kinetic and thermodynamic profile ( $\Delta G^{\ddagger} = 31.6$ ;  $\Delta G =$ +5.3 kcal mol<sup>-1</sup>). 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 quite endergonic ( $\Delta G$  = +4.4 kcal  $mol^{-1}$ ). Most excitingly, it was uncovered that the 4phenyl group dramatically impacted the kinetics and thermodynamics: the [3,3] has a barrier of 22.9 kcal mol<sup>-1</sup> ( $\Delta G^{\ddagger}$ ) and is ~isoenergetic ( $\Delta G = +0.17$  kcal mol<sup>-1</sup>). Thus, the reaction appears to be fluxional/shape-shifting at room temperature.36-40

For this substrate, we also modelled the *dissociative* pathway (Scheme 2D). It was found that bond breakage to two allylic radical intermediates is a higher energy process than the concerted transition state (Scheme 2C *vs.* Scheme 2D). Specifically, the dissociative pathway was found to be kinetically less favourable ( $\Delta G^{\ddagger} \sim 27.6$  kcal mol;  $\Delta G = 26.2$  kcal mol<sup>-1</sup>) than the concerted process ( $\Delta G^{\ddagger} = 22.9$  kcal mol<sup>-1</sup>). While the dissociative pathway is less favourable than the concerted transformation, we surmised that the two-step process becomes accessible at elevated temperature (*vide infra*). Finally, the ionic pathway was calculated to be significantly higher for this substrate (see the ESI<sup>†</sup>).

The class of substrate uncovered from our computational investigation could be accessed from γ,γ-dimethylalkylidenemalononitrile (7a) and 1,3-diarylallyl electrophiles (such as 8a) by Pd-catalyzed deconjugative allylic alkylation (Scheme 3A).<sup>33</sup> 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). To determine whether the transformation was progressing through the predicted concerted pathway (Scheme 2C) over the dissociative pathway (Scheme 2D), substrate 5b was prepared by an analogous deconjugative allylic alkylation reaction. Similarly, two Cope equilibrium isomers 5b and 6b are observed at room temperature in a 12:88 ratio. Upon heating at 100 °C for 3 h, the 1,5-dienes "scramble" (e.g. iso-6b is observed; 0.2:1.0:1.5 ratio of 5b:6b:iso-6b) indicating that the dissociative pathway is only accessible at elevated temperature. This is all in good agreement with the calculated kinetics and thermodynamics of this system (Scheme 2).

With respect to the synthetic methodology, we aimed to increase the overall efficiency and applicability of the sequence (Scheme 3B). Specifically, we wanted to avoid [3,3] equilibrium mixtures and sensitive/unstable substates and intermediates. 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<sub>3</sub>)<sub>4</sub>. When the coupling was complete, methanol and NaBH<sub>4</sub> were added to drive the Cope equilibrium forward, yielding the reduced Cope rearrangement product **10a** in 76% isolated yield. 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  $4^{\circ}/3^{\circ}$  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).<sup>41,42</sup> 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





Scheme 2 Computational analysis of 3,3-dicyano-1,5-diene that in theory could result in vicinal  $4^{\circ}/3^{\circ}$  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) The dissociative mechanism for substrate 5 is higher than the closed transition state. (E) visualization of the kinetic- and thermodynamic differences of transformations (A–D).

![](_page_2_Figure_4.jpeg)

Scheme 3 (A) Observation of fluxional [3,3] and confirmation of calculated predictions. (B) Optimization of a reductive Cope rearrangement protocol for constructing vicinal  $4^{\circ}/3^{\circ}$  centers. (C) The Pd-catalyzed deconjugative allylic alkylation must be regioselective.

nucleophile reacts preferentially at the  $\alpha$ -position and the electrophile reacts at the allylic position bearing the donorarene (Scheme 3C).<sup>41,42</sup> 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 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 (**101–10q**). For example, 3-chloro-4-pyridyl (**101/10m**) 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

![](_page_3_Figure_2.jpeg)

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

![](_page_3_Figure_4.jpeg)

![](_page_3_Figure_5.jpeg)

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**).

Scheme 6 (A) oxidative amidation of malononitrile. (B) Removal of "activating group" by ozonolysis.

The phenyl or the *p*-methoxyphenyl group is necessary to achieve the  $4^{\circ}/3^{\circ}$  carbon-generating Cope rearrangement: it functions as an "activator" by lowering the kinetic barrier and increasing thermodynamic favourability. 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).28,43 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<sup>34</sup> to products 12 containing a dense array of pharmaceutirelevant functionalities (amides, callv gem-dimethyl, fluoroaromatics, and heteroaromatics). Following this transformation, ozonolysis terminated with a NaBH<sub>4</sub> quench installs an alcohol moiety on small molecule 13a.

These first computational and experimental studies utilizing 3,3-dicyano-1,5-dienes as substrates for constructing vicinal  $4^{\circ}/3^{\circ}$  centers sets the stage for much further examination and application. For example, while we focused our efforts on *gem*-dimethyl-based quaternary carbons, it is likely that *other* functionality can be installed at this position. For example, while unoptimized, it appears the protocol is reasonably effective at incorporating a piperidine moiety in addition to heteroarenes

![](_page_4_Figure_4.jpeg)

Scheme 7 (A) The construction of 4/3° centres on piperidines. (B) Promoting endergonic [3,3] rearrangements is possible, assuming the [3,3] kinetic barrier is sufficiently low.

While the 4,6-diaryl-3,3-dicyano-1,5-dienes offered the most attractive energetic profile (low kinetic barrier, isoenergetic [3,3] equillibrium; Scheme 2C), the 4-methyl analogue is also intriguing to consider as a viable substrate class for reductive Cope rearrangement (Scheme 2B). The challenge here is that the kinetics and thermodynamics are quite unfavourable (not observable by NMR), but potentially not prohibitively so. It is extremely exciting to find that Cope equilibria that are significantly endergonic in the desired, forward direction (*e.g.* **3a** to **4a**) can be promoted by a related reductive protocol (Scheme 7B). While unoptimized, we were able to isolate product **17** in *xx*% yield by heating at 90 °C in the presence of Hantzsch ester in DMF.

### Conclusions

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 ( $\Delta G^{\ddagger} \sim 23$  kcal mol<sup>-1</sup>,  $\Delta G \sim 0$  kcal mol<sup>-1</sup>) and reductive conditions are utilized to drive the rearrangement forward, toward products containing a central *gem*-dimethyl/arene motif flanked on either side by a malono-nitrile 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.

#### Data availability

The data is already shared in the ESI.†

### Author contributions

Kristin Sobie led the experimental studies outlined in this work. Matthew Albritton initiated the computational and experimental studies outlined in this work. Yinuo Yang performed computational analyses associated with this work. Mariana Alves performed experimental studies associated with this work. Adrian E. Roitberg led and mentored the computational team and co-wrote the manuscript. Alexander J. Grenning led and mentored the experimental team and co-wrote the manuscript.

# Conflicts of interest

There are no conflicts to declare.

# Acknowledgements

We thank the NIH NIGMS for financial support (R35 GM137893-01). This material is based upon work supported by the National Science Foundation (NSF CAREER 1844443). We thank the ACS Division of Organic Chemistry for a Summer Undergraduate Research Fellowship (SURF) (MA and AJG). We thank the Mass Spectrometry Research and Education Center and their funding source: NIH S10 OD021758-01A1. We acknowledge the University of Florida – Research Computing for providing computational resources and support that have contributed to the results reported in this publication.

## Notes and references

- 1 G. Wu, J.-R. Wu, Y. Huang and Y.-W. Yang, *Chem.-Asian J.*, 2021, **16**, 1864–1877.
- 2 F. Zhou, L. Zhu, B.-W. Pan, Y. Shi, Y.-L. Liu and J. Zhou, *Chem. Sci.*, 2020, **11**, 9341–9365.
- 3 Z. Wang, Org. Chem. Front., 2020, 7, 3815-3841.
- 4 Y. Li and S. Xu, Chem.-Eur. J., 2018, 24, 16218-16245.
- 5 J. Feng, M. Holmes and M. J. Krische, *Chem. Rev.*, 2017, **117**, 12564–12580.
- 6 C. Schneider and C. F. Weise, in *Compr. Org. Synth*, Elsevier B.V., 2nd edn, 2014, pp. 867–911.
- 7 M. Hiersemann and T. Jaschinski, in *Compr. Chirality*, Elsevier B.V., 2012, pp. 625–647.
- 8 L. A. Paquette, Tetrahedron, 1997, 53, 13971-14020.
- 9 M. Simek, K. Bartova, R. Pohl, I. Cisarova and U. Jahn, *Angew. Chem., Int. Ed.*, 2020, **59**, 6160–6165.
- 10 D.-S. Hsu and C.-C. Liao, Org. Lett., 2003, 5, 4741-4743.
- 11 E. J. Corey and R. S. Kania, *Tetrahedron Lett.*, 1998, **39**, 741–744.
- 12 W.-C. Liu and C.-C. Liao, Synlett, 1998, 912-914.
- 13 T.-H. Lee and C.-C. Liao, *Tetrahedron Lett.*, 1996, **37**, 6869–6872.
- 14 R. C. Gadwood and R. M. Lett, *J. Org. Chem.*, 1982, 47, 2268–2275.
- 15 S. Kruger and T. Gaich, *Beilstein J. Org. Chem.*, 2014, **10**, 163–193.
- 16 D. Garayalde, K. Krueger and C. Nevado, *Angew. Chem., Int. Ed.*, 2011, **50**, 911–915.
- 17 K. Miki, K. Ohe and S. Uemura, *J. Org. Chem.*, 2003, **68**, 8505–8513.
- 18 S. Yokoshima, H. Tokuyama and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2000, **39**, 4073–4075.
- 19 T. Fukuyama and G. Liu, J. Am. Chem. Soc., 1996, **118**, 7426–7427.
- 20 E. Piers, M. Jean and P. S. Marrs, *Tetrahedron Lett.*, 1987, 28, 5075–5078.

- 21 R. J. Felix, D. Weber, O. Gutierrez, D. J. Tantillo and M. R. Gagné, *Nat. Chem.*, 2012, 4, 405–409.
- 22 Y. Qiao, S. Kumar and W. P. Malachowski, *Tetrahedron Lett.*, 2010, **51**, 2636–2638.
- 23 T. Paul, W. P. Malachowski and J. Lee, *J. Org. Chem.*, 2007, 72, 930–937.
- 24 W. P. Malachowski, T. Paul and S. Phounsavath, J. Org. Chem., 2007, 72, 6792–6796.
- 25 T. Paul, W. P. Malachowski and J. Lee, Org. Lett., 2006, 8, 4007-4010.
- 26 D. C. Wigfield, S. Feiner, G. Malbacho and K. Taymaz, *Tetrahedron*, 1974, **30**, 2949–2959.
- 27 E. Fereyduni and A. J. Grenning, *Org. Lett.*, 2017, **19**, 4130–4133.
- 28 E. Fereyduni, J. N. Sanders, G. Gonzalez, K. N. Houk and A. J. Grenning, *Chem. Sci.*, 2018, **9**, 8760–8764.
- 29 S. K. Scott, J. N. Sanders, K. E. White, R. A. Yu, K. N. Houk and A. J. Grenning, *J. Am. Chem. Soc.*, 2018, **140**, 16134– 16139.
- 30 P. Vertesaljai, R. Serrano, M. D. Mannchen, M. Williams, E. Semenova and A. J. Grenning, *Org. Lett.*, 2019, 21, 5704– 5707.
- 31 E. Fereyduni, O. Lahtigui, J. N. Sanders, B. M. Tomiczek, M. D. Mannchen, R. A. Yu, K. N. Houk and A. J. Grenning, *J. Org. Chem.*, 2021, **86**, 2632–2643.
- 32 E. G. Foster, A. C. Cope and F. Daniels, *J. Am. Chem. Soc.*, 1947, **69**, 1893–1896.
- 33 H. Nakamura, H. Iwama, M. Ito and Y. Yamamoto, J. Am. Chem. Soc., 1999, 121, 10850–10851.
- 34 J. Li, M. J. Lear and Y. Hayashi, Angew. Chem., Int. Ed., 2016, 55, 9060–9064.
- 35 T. T. Talele, J. Med. Chem., 2018, 61, 2166–2210.
- 36 O. Yahiaoui, L. F. Pasteka, B. Judeel and T. Fallon, Angew. Chem., Int. Ed., 2018, 57, 2570–2574.
- 37 J. F. Teichert, D. Mazunin and J. W. Bode, J. Am. Chem. Soc., 2013, 135, 11314–11321.
- 38 O. Yahiaoui, L. F. Pasteka, C. J. Blake, C. G. Newton and T. Fallon, Org. Lett., 2019, 21, 9574–9578.
- 39 H. D. Patel, T.-H. Tran, C. J. Sumby, L. F. Pasteka and T. Fallon, J. Am. Chem. Soc., 2020, 142, 3680–3685.
- 40 Y.-Y. Ma, M. Yan, H.-R. Li, Y.-B. Wu, X.-X. Tian, H.-G. Lu and S.-D. Li, *Sci. Rep.*, 2019, **9**, 1–8.
- 41 M. Moreno-Manas and J. Ribas, *Tetrahedron Lett.*, 1989, **30**, 3109–3112.
- 42 M. Prat, J. Ribas and M. Moreno-Manas, *Tetrahedron*, 1992, **48**, 1695–1706.
- 43 O. Lahtigui, F. Emmetiere, W. Zhang, L. Jirmo, S. Toledo-Roy, J. C. Hershberger, J. M. Macho and A. J. Grenning, *Angew. Chem., Int. Ed.*, 2016, 55, 15792–15796.