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Overcoming Kinetic and Thermodynamic Challenges of Classic Cope Rearrangements

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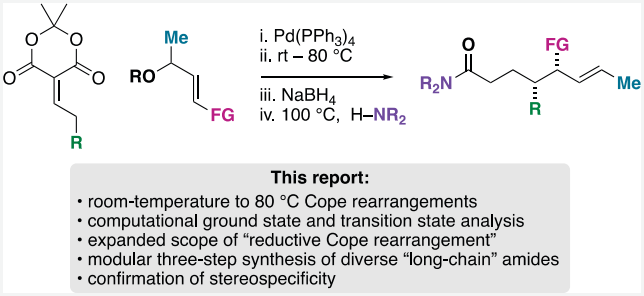
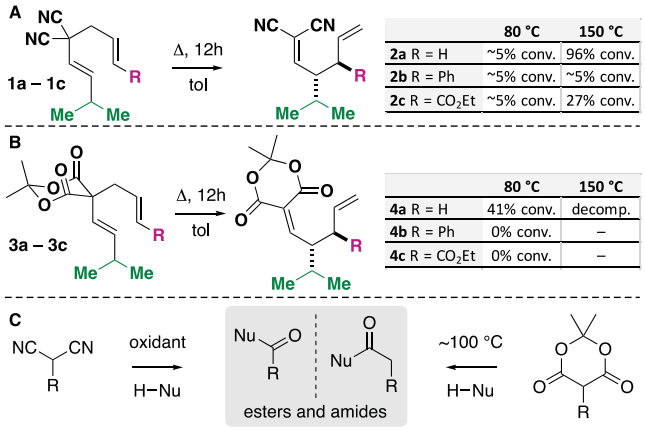
ABSTRACT: Systematic evaluation of 1,5-dienes bearing 3,3-electron-withdrawing groups and 4-methylation results in the discovery of a Cope rearrangement for Meldrum's acid-containing substrates that have unexpectedly favorable kinetic and thermodynamic profiles. The protocol is quite general due to a concise and convergent synthesis from abundant starting materials. Furthermore, products with an embedded Meldrum's acid moiety are prepared, which, in turn, can yield complex amides under neutral conditions. We have now expanded the scope of the reductive Cope rearrangement, which, via chemoselective reduction, can promote thermodynamically unfavorable [3,3] sigmatropic rearrangements of 3,3-dicyano-1,5-dienes to form reduced Cope rearrangement products. The Cope rearrangement is found to be stereospecific and can yield enantioenriched building blocks when chiral, nonracemic 1,3-disubstituted allylic electrophiles are utilized. We expand further the use of Cope rearrangements for the synthesis of highly valuable building blocks for complex- and drug-like molecular synthesis.



INTRODUCTION

The original Cope rearrangement substrates often contained 3,3-dicyano-1,5-diene core structures.[1,2] They thermally react commonly at temperatures >150 °C to yield γ-allyl alkylidenemalononitriles. In addition to the high kinetic barrier, these reactions are often thermodynamically unfavorable (Scheme 1A). For example, while the 6-unsubstituted substrate (**1a**) undergoes clean transformation to the desired product (**2a**) at 150 °C, the substituted variants (**1b** and **1c**) do not.[3] Nevertheless, the transformation is often successful and yields 1,5-dienes bearing a malonic acid variant.[4−11] We hypothesize that 1,5-dienes bearing a Meldrum's acid moiety at the 3-position could have improved synthetic utility considering the versatility of Meldrum's acid.[12−16] For example, malononitrile can be converted to esters and amides by oxidative decyanation,[17−19] but Meldrum's acid undergoes functional group interconversion to esters or amides by simple thermal treatment in the presence of a heteroatomic nucleophile (Scheme 1C). Such Meldrum's acid-containing 1,5-dienes have yet to be reported, likely due to the following additional challenge: Meldrum's acid derivatives undergo retro-[2 + 2 + 2] cycloaddition at temperatures >90 °C, yielding a ketene, CO_2, and acetone (Scheme 1C). This sets up a chemoselectivity issue for competing thermal transformations resulting in a limit as to how high Meldrum's acid-containing 1,5-dienes can be heated (Scheme 1B). While conversion was observed to some extent for **3a** → **4a** at 80 °C, the substrate

Scheme 1. (A, B) Challenges Associated with Nitrile- and Meldrum's Acid-Containing 1,5-Dienes and (C) Malononitrile and Meldrum's Acid Have a Complementary Value as Functional Groups



	80 °C	150 °C
2a R = H	~5% conv.	96% conv.
2b R = Ph	~5% conv.	~5% conv.
2c R = CO_2Et	~5% conv.	27% conv.

	80 °C	150 °C
4a R = H	41% conv.	decomp.
4b R = Ph	0% conv.	–
4c R = CO_2Et	0% conv.	–

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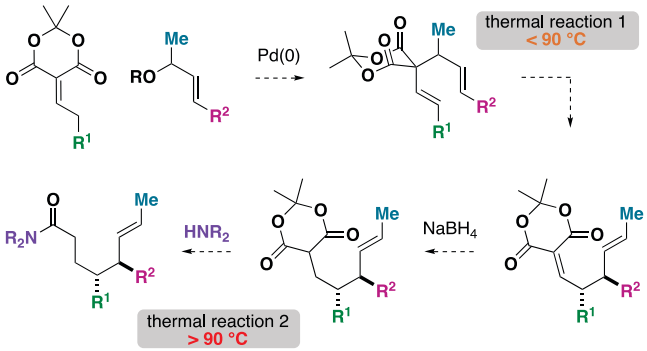
completely decomposed at elevated temperatures (150 °C). Additionally, the more sterically congested 6-substituted 1,5-dienes **3b**−**3c** that would yield more complex, vicinal stereogenic products **4b**−**4c**, respectively, did not react at all at the lower temperature.

The kinetic and thermodynamic challenges associated with 3,3-Meldrum's acid-containing 1,5-dienes, if overcome, would allow for sequenced thermal transformations (Scheme 2): if a

Scheme 2. Summary of This Work: Reordering of Preference for Thermal Reactivity Results in a Simple Route to Complex Amides

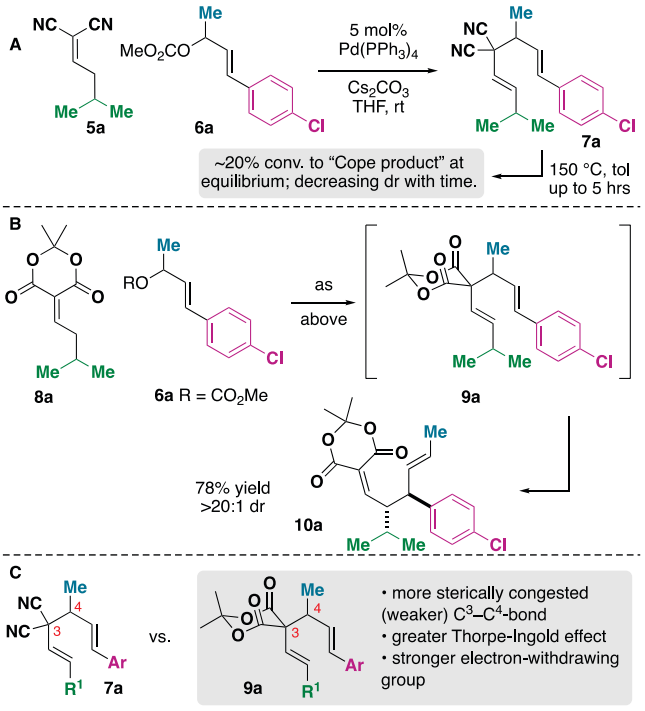


class of 1,5-diene substrates could be identified that proceeds with a reversal of preference for sequenced thermal reactivity ([3,3] first, then Meldrum's acid retro-[2 + 2 + 2]), then a modular route to complex amides could be achieved, among other applications. Such a sequence would be of significant value considering the simplicity of thermal reactions and the value of amides in drug discovery.[20] We now report that the Pd-catalyzed allylic alkylation[21,22] between alkylidene Meldrum's acid pronucleophiles and 1,3-disubstituted allylic electrophiles[23−29] yields 1,5-dienes that are generally reactive toward Cope rearrangement at temperatures ranging from a room temperature of −80 °C, well below the temperature at which Meldrum's acid derivatives decompose. The result is a general synthesis of relatively complex chiral amides from simple Meldrum's acid derivatives (Scheme 2).

RESULTS AND DISCUSSION

We previously reported that 1,5-dienes derived from alkylidenemalononitrile and 1,3-diarylallyl electrophiles (chalcone derivatives) undergo room-temperature Cope rearrangement.[9] We also recently reported that thermodynamically unfavorable Cope rearrangements can be driven forward by chemoselective in situ reduction.[8,10] We have now examined the significance of the 3,3-electron-withdrawing group and 4-methylation on the favorability of allylic transposition. This study was based on the following initial observations (Scheme 3): 1,5-diene **7a** (derived from the alkylidenemalononitrile **5a** and 3-chlorophenyl-1-methylallylcarbonate **6a** via Pd-catalyzed regioselective deconjugative allylation) was poorly reactive to Cope rearrangement at 150 °C in toluene (~20% conv. at equilibrium; decreasing diastereomeric ratio with time). The analogous Meldrum's acid scaffold **9a** (derived from **8a** and **6a**) converted to the Cope product **10a** transiently at room temperature with complete conversion, high diastereoselectivity, and good isolated yield. In the course of the Pd-catalyzed regioselective deconjugative allylation, 1,5-diene **9a** was observed in crude NMRs, but following workup and

Scheme 3. (A, B) Initial Observation on the Synergistic Influence of 3-Meldrum's Acid and 4-Methylation on Cope Rearrangement Favorability and (C) Why Are 3,3-Meldrum's Acid−4-Methyl-1,5-dienes So Reactive?



chromatography, only the Cope product **10a** was isolated. As can be seen in the comparison of **7a** and **9a**, there is a significant difference in thermodynamic favorability by the change in the electron-withdrawing group.

The kinetic and thermodynamic favorability is a synergistic effect between 3,3-Meldrum's acid and 4-methylation (Scheme 3C). To reiterate, changing from Meldrum's acid to malononitrile (Scheme 3) or removing the 4-methyl group (Scheme 1A,B) results in significantly less reactive substrates. This surprising rate enhancement is likely the result of several physical organic factors: (a) an increased conformation bias for the reactive σ-cis conformer (e.g. Thorpe−Ingold effect[30]), (b) a weaker C3−C4 bond due to increased steric bulk at the vicinal quaternary/tertiary centers, and (c) the greater electron-withdrawing ability of Meldrum's acid moiety.[31]

To gain a better understanding of the reactivity of this class of 1,5-dienes, we performed density functional theory computations to obtain the free-energy profiles of the Cope rearrangement of malononitrile derivative **7a** and Meldrum's acid derivative **9a** (Scheme 4). The computations reveal that the two Cope rearrangements have nearly identical kinetic profiles: malononitrile derivative **7a** has a Cope rearrangement barrier of 25.7 kcal/mol, while Meldrum's acid derivative **9a** has a Cope rearrangement barrier of 25.0 kcal/mol, and both transition states have similar partial bond lengths and overall geometries. These results suggest that the difference in reactivity between malononitrile derivative **7a** and Meldrum's acid derivative **9a** stems primarily from thermodynamic, rather than kinetic, factors. Indeed, the Cope rearrangement of Meldrum's acid derivative **9a** is thermodynamically favorable (ΔG = −4.7 kcal/mol), primarily owing to the enthalpically favorable development of additional conjugation with Meldrum's acid moiety (ΔH = −5.1 kcal/mol). The Cope

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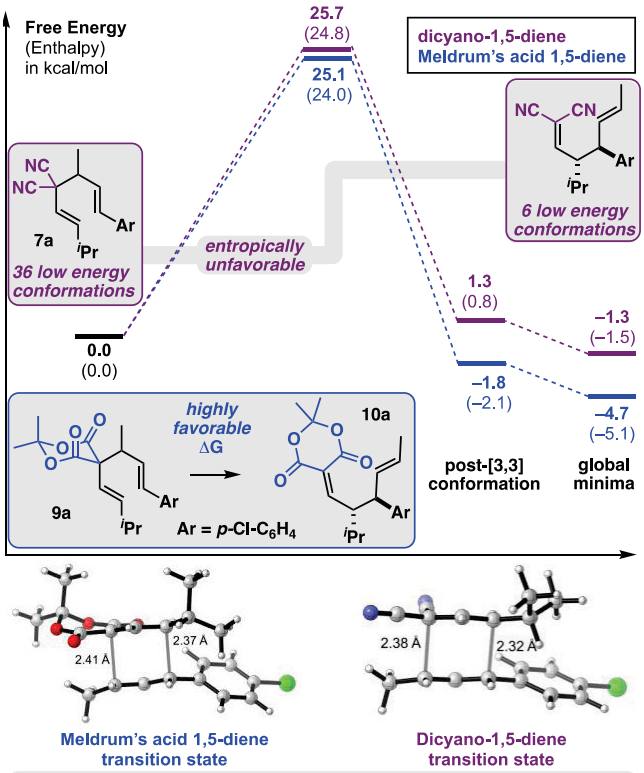
Scheme 4. Computational Analysis of the Cope Rearrangement of Meldrum's Acid- and Malononitrile-Containing 1,5-Dienes



Optimization: M06-2X / 6-31+G(d) / CPCM(THF)
Single Point Energies: M06-2X / 6-311++G(2d,2p) / CPCM(THF)
Thermochemistry: 25 °C and 1 M with Truhlar corrections for frequencies above 100 cm^{-1}

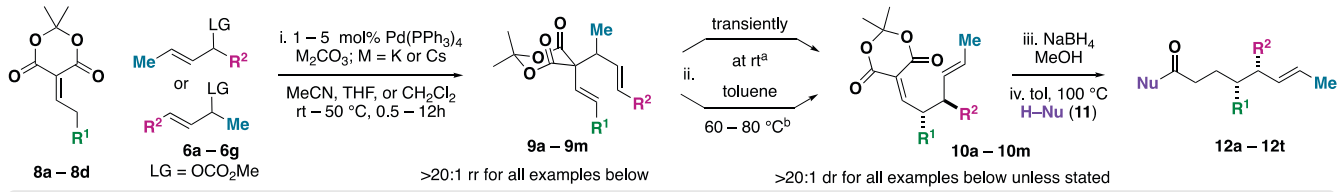
rearrangement of malononitrile derivative **7a** involves instead the development of additional conjugation with the malononitrile moiety, which is also enthalpically favorable, but according to the computations, by a smaller amount (ΔH = −1.5 kcal/mol). Moreover, the computed energy difference (ΔG = −1.3 kcal/mol) reflects only the free-energy difference between single conformations of the starting material and the product. However, we find that there are relatively few low-lying product 1,5-diene conformations (6 conformations within 1.4 kcal/mol of the global minimum) compared to starting material 1,5-diene conformations (36 conformations within 1.4 kcal/mol of the global minimum), meaning that the ensemble of starting material conformers has higher conformational entropy than the ensemble of product conformers. This suggests that the Cope rearrangement of malononitrile derivative **7a** is entropically disfavored, primarily owing to conformational entropy differences, resulting in the observed overall thermoneutral ΔG.

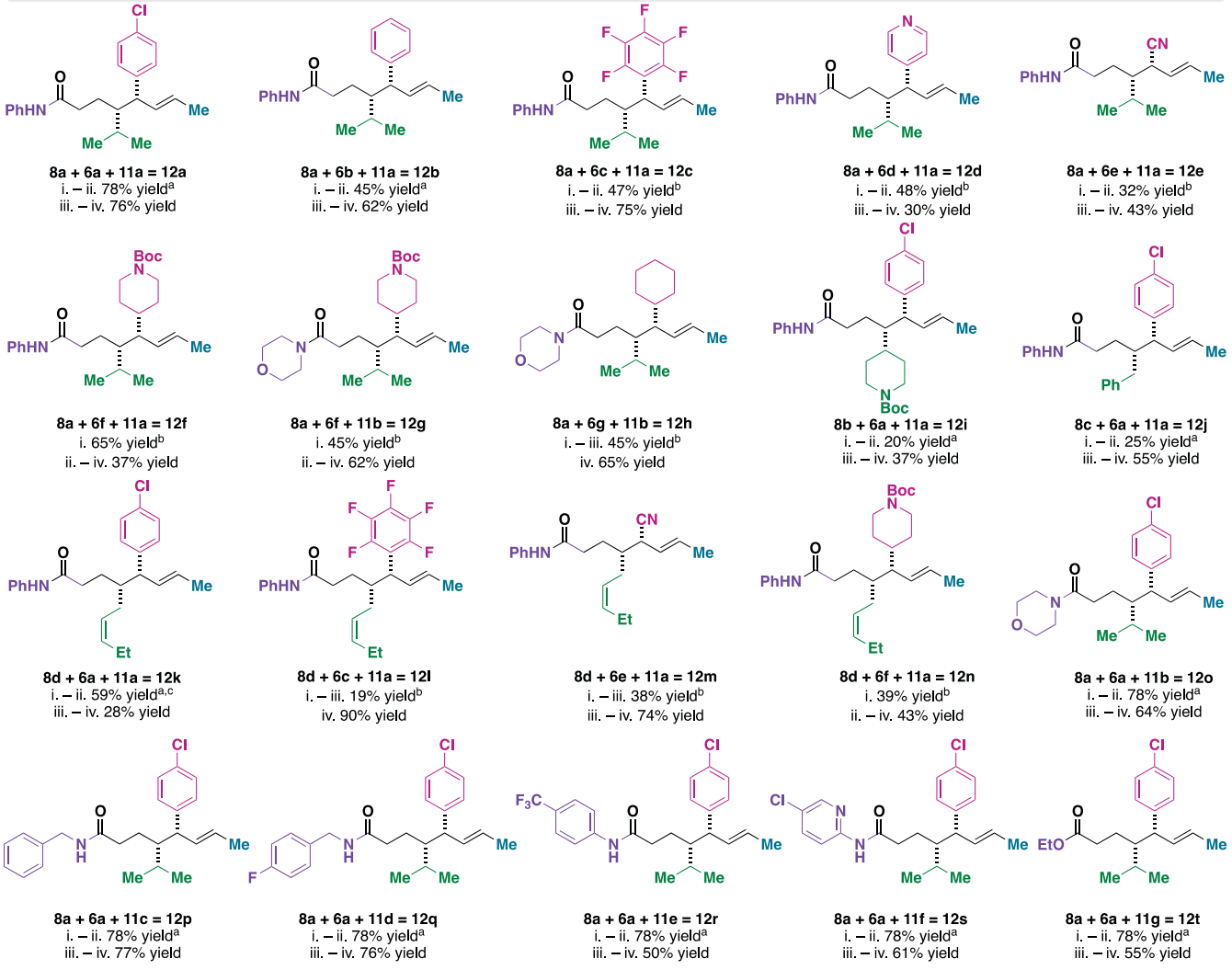
Having established an understanding for the deconjugative alkylation/Cope rearrangement sequence, we set out to demonstrate that complex amides can be prepared in a simple convergent fashion via a protocol where thermal Cope rearrangement and then thermal Meldrum's acid functional group interconversion play a key role. Specifically, from Meldrum's acid-derived Knoevenagel adducts **8a**−**8d**, allylic electrophiles **6a**−**6g**, $NaBH_4$, and an amine (or ethanol, **11a**−**11g**) (Scheme 5), highly complex amides **12a**−**12s** (and an ester, **12t**) were prepared concisely: three steps if the Cope rearrangement occurred transiently and four if not. Because the starting materials are easily available and the synthetic sequence is straightforward and brief, it is easy to achieve modular amide synthesis, often with limited purifications in the sequence. For example, **12a**−**12h** were prepared from alkylidene Meldrum's acids **8a**−**8d** and a series of diverse allylic electrophiles obtained from readily available building blocks. By modulation of the starting allylic electrophile (**6a**−**6d**), a variety of arenes including 4-chlorophenyl (**12a**), phenyl (**12b**), pentafluorophenyl (**12c**), and 4-pyridyl (**12d**) were incorporated into the products. Using crotonaldehyde cyanohydrin (**6e**), a nitrile functional group was installed on the scaffold yielding **12e**. Finally, it was also found that 1,3-dialkylallyl electrophiles (**6f**−**6g**) react regioselectively to ultimately yield amides bearing 4-*N*-Boc-piperidyl (**12f**−**12g**) and cyclohexyl (**12h**) groups at the vicinal stereocenters. With respect to the scope of the alkylidene Meldrum's acid **8**, products derived from isovaleraldehyde (**12a**−**12h**), *N*-Boc-piperidine carboxaldehyde (**12i**), hydrocinnamaldehyde (**12j**), and *cis*-4-heptenal (**12k**) were prepared in a range of yields. Notably, this protocol was optimized for the isovaleraldehyde substrate (**8a**). Furthermore, **8a** could easily be prepared in large quantities and was bench-stable. In general, other Knoevenagel adducts **8b**−**8d** were less stable, which potentially accounts for the decreased yields through the coupling/Cope rearrangement sequence. That said, we optimized the synthesis of **8d**, and when used fresh in toluene, we noticed a dramatic improvement in yield (standard conditions with "older" samples of **8d** resulted in modest yields of product (ca. 19%)). Thus, in many cases, it is prudent to use the alkylidene Meldrum's acid derivatives directly after their preparation and/or take extra precaution in their storage. On this line, examples **12k**−**12n** show a scope study of **8d** with a variety of allylic electrophiles (**6a**, **6c**, **6e**, and **6f**). The final series of products **12o**−**12t** in Scheme 5 were prepared from **8a**, **6a**, and a series of nucleophiles (**11a**−**11g**) that react thermally with Meldrum's acid moiety.

Attempts at coupling the *ortho*-chlorophenylallyl electrophile **6h** with the isovaleraldehyde−Meldrum's acid adduct **8a** resulted in isomeric mixtures of products (Scheme 6). However, the 2,6-dichlorophenylallyl electrophiles **6i** and **8a** were highly competent coupling partners yielding **13a**, exhibiting the opposite regioselectivity of that observed in Scheme 5. The result might suggest a different reaction manifold that does not involve Cope rearrangement: we propose that a direct regioselective γ-allylation is likely operative as steric shielding would be minimized. Similar to the previous examples in Scheme 5, **13a** was converted to amide **13b** by alkylidene Meldrum's acid reduction and thermal amidation.

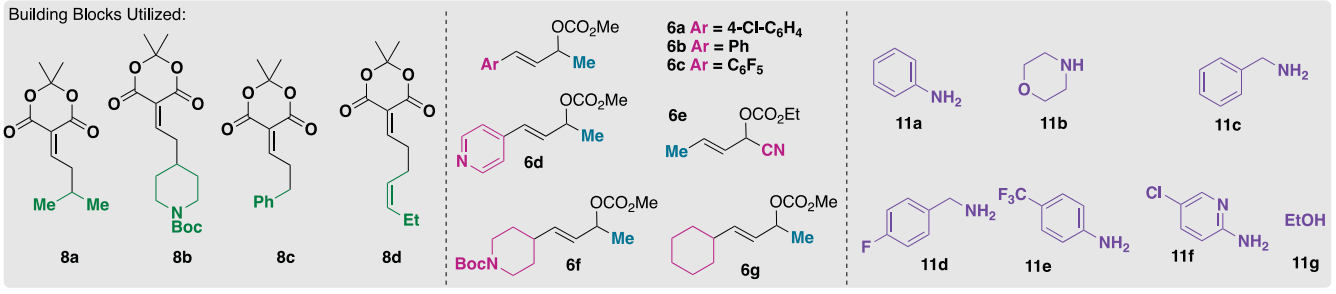
The unique combination of 3,3-Meldrum's acid and 4-methylation onto 1,5-diene architectures allows for kinetic and thermodynamically favorable Cope rearrangements to occur. As alluded to in this work, the analogous 3,3-dicyano variants are not nearly as reactive for both kinetic (150 °C activation temperature) and thermodynamic (1,5-diene mixtures observed at equilibrium) reasons. For example, a series of 3,3-dicyano-1,5-dienes with different 6-substituents when heated at 150 °C resulted in varied thermodynamic favorability (Scheme 7). For example, the 6-chlorophenyl substrate (**7a**) was unreactive to Cope rearrangement. Interestingly, 6-cyano- (**7b**) and 6-ester (**7c**)-containing substrates underwent Cope rearrangement with high conversion. Finally, a 6-aliphatic

Scheme 5. Complex Amide Synthesis by Sequenced Thermal Transformations





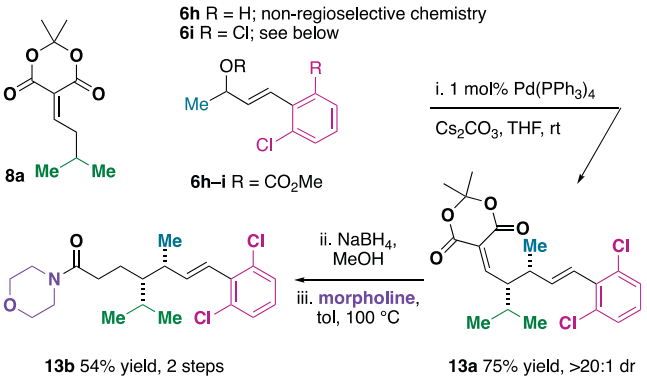
[a] Cope rearrangement to **10** occurs transiently [b] the deconjugative alkylation product is isolated and heated to yield products **10**. [c] 19% yield under the "standard conditions". 59% yield was achieved by performing the transformation in toluene in lieu of THF.



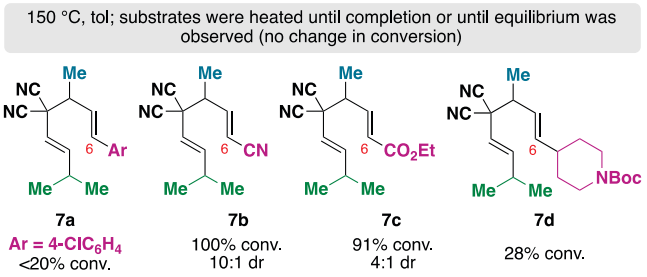
substrate (**7d**) was poorly reactive toward Cope rearrangement conditions.

Our next goal was to extend the scope of the Cope rearrangement to 3,3,-dicyano-4-methyl-1,5-dienes with variable groups at the 1- and 6-positions. We recently reported that 3,3-dicyano-1,5-dienes with poor thermodynamic favorability can be promoted to reduced Cope products via chemoselective reduction of the in situ generated alkylidenemalononitrile with Hantzsch amide.[8,10] As shown in Scheme 8, this strategy was generally effective for this previously unreported class of 1,5-

Scheme 6. Change in Regioselectivity with a 2,6-Dichlorophenyl Electrophile 6i



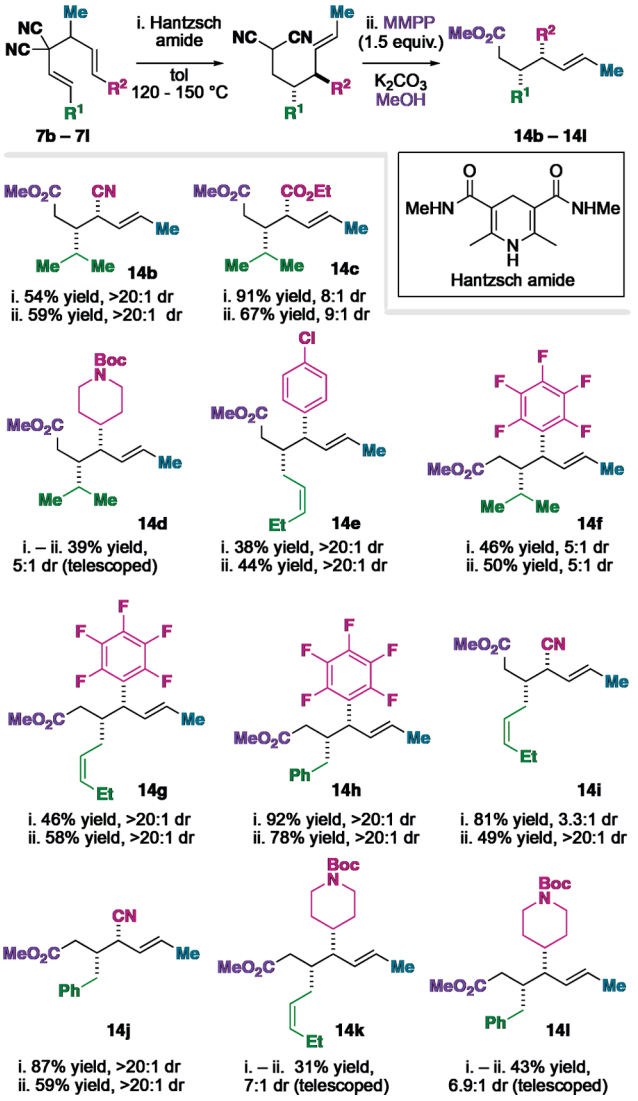
Scheme 7. 6-"Functional Group"-4-methyl-3,3-dicyano-1,5-dienes Are Poor Thermal Cope Rearrangement Substrates



diene.[10] Of the initial substrates examined for thermal Cope rearrangement reactivity (**7a**–**7d**), **7b**–**7d** underwent clean reductive Cope rearrangement and could be converted to complex esters **14b**–**14d** via malononitrile oxidative esterification (MMPP, magnesium monoperoxyphthalate[17]) (Scheme 8). While **7b** and **7c** already have favorable thermodynamic profiles, we did notice an increase in diastereoselectivity when performing the reductive Cope rearrangement. Thus, the reduction step is occurring faster than epimerization. While **7a** was unreactive, a variety of other styrene-containing substrates (**7e**–**7h**) could be transformed via reductive Cope rearrangement and converted to esters **14e**–**14h** by oxidative decyanation. Finally, additional nitrile (**14i**–**14j**) and *N*-Boc-piperidine (**14k**–**14l**)-containing esters were prepared successfully in good to excellent yields and diastereoselectivity via the two-step procedure.

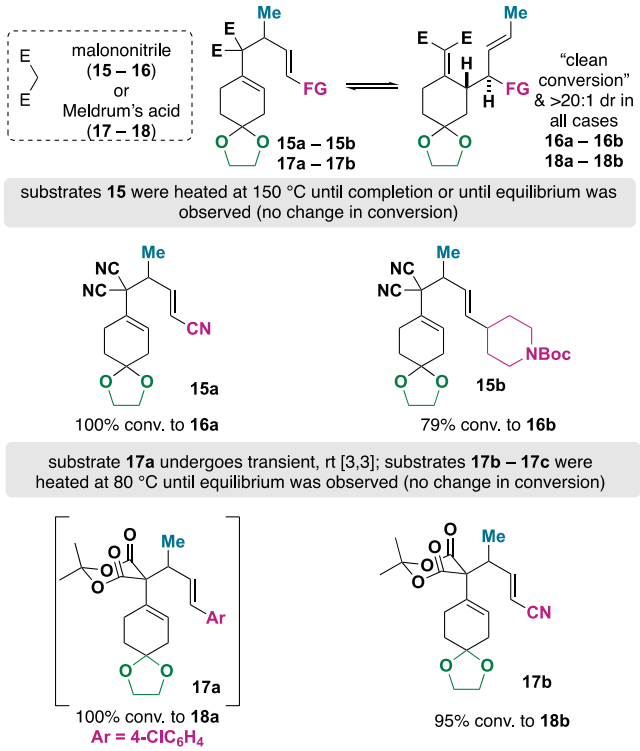
Having found that aldehyde-derived 3,3-Meldrum's acid–4-methyl-1,5-dienes have exceptional kinetic and thermodynamic profiles (Scheme 3) and that the analogous 3,3-dicyano-4-methyl-1,5-dienes can be promoted via the reductive Cope protocol, the final set of 1,5-dienes to explore for Cope rearrangement reactivity were ketone derivatives (Scheme 9). A series of malononitrile- (**15a**–**15b**) and Meldrum's acid (**17a**–**17b**)-containing 1,5-dienes for rearrangement to **16** and **18**, respectively, were examined. We were pleased to find that across the full series, there was high thermodynamic favorability in that all compounds reached high conversion. Notably, the malononitrile series (**15**) required heating to 150 °C, whereas Meldrum's acid series (**17**) underwent Cope rearrangement at lower temperatures (rt –80 °C). This is a similar trend to that observed in the aldehyde-based studies above.

Scheme 8. 6-"Functional Group"-4-methyl-3,3-dicyano-1,5-dienes Undergo Reductive Cope Rearrangement and Oxidative Decyanation to Yield Complex Esters

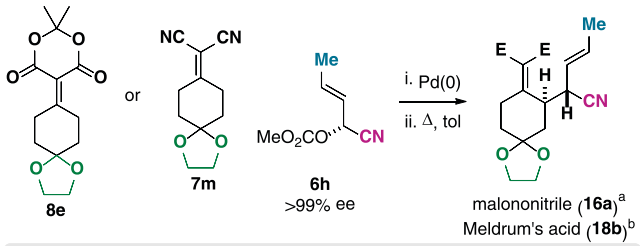


We next examined the stereoselectivity of the deconjugative alkylation and Cope rearrangement steps (Scheme 10). Based on the literature, enantioenriched 1,3-disubstituted allylic electrophiles should undergo stereospecific allylic alkylation via a double inversion mechanism.[23−29] Through the closed nature of the Cope rearrangement transition state, this stereocenter should be relayed into a Cope rearrangement product bearing vicinal stereocenters.[32] To probe this, we prepared the nitrile-containing allylic electrophile enantioenriched by a well-precedented asymmetric transformation, whereby almond meal provided the necessary biocatalysts.[33,34] Under the standard conditions, it was found that the stereochemistry from the allylic electrophile could indeed be transposed through the alkylation and Cope rearrangement sequence with high conservation of *ee* for both Meldrum's acid and malononitrile-derived Knoevenagel adducts. The stereoselectivity for the sequence can be ascribed to a double inversion mechanism on **6h** via [**I-a**] followed by a diastereoselective Cope rearrangement via the proposed Zimmerman–Traxler transition state [**I-b**] (Scheme 11). The slight erosion of enantiomeric excess in the process can be

Scheme 9. Ketone-Derived 3,3-Malononitrile- and Meldrum's Acid-Containing 1,5-Dienes Have High Thermodynamic Favorability



Scheme 10. Enantiospecific Allylic Alkylation/[3,3] Rearrangement



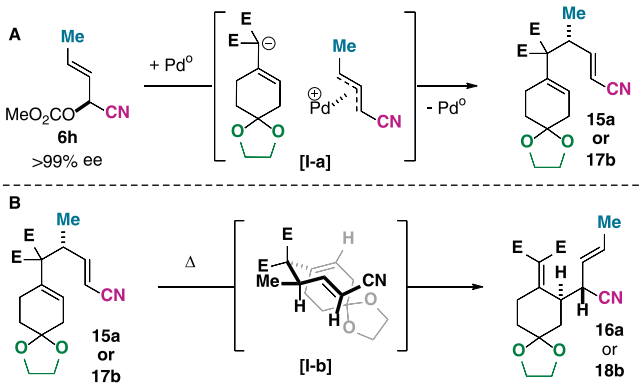
[a] for malononitrile (**7m**): i. 1 mol% $Pd(PPh_3)_4$ K_2CO_3, CH_2Cl_2 (66% yield) ii. 150 °C, tol, 15 min. (74% yield, >20:1 dr, 93% ee)
[b] for Meldrum's acid (**8e**): i. 1 mol% $Pd(PPh_3)_4$ K_2CO_3, MeCN (66% yield) ii. 80 °C, tol, 4 h. (65% yield, >20:1 dr, 95% ee)

rationalized by a nucleophilic displacement by Pd(0) on the Pd-π-allyl intermediate.[35]

CONCLUSIONS

Through the systematic analysis of 1,5-dienes derived by deconjugative alkylation between Knoevenagel adducts and 1,3-disubstituted electrophiles, we have uncovered surprisingly mild Cope rearrangements of 3,3-Meldrum's acid-containing 1,5-dienes and expanded the scope of our reductive Cope rearrangement protocol. The synthesis of Meldrum's acid-containing products is particularly valuable considering the ease of functional group interconversions of Meldrum's acid moiety. We have reported the preparation of a range of complex amides and esters by thermal functional group interconversions under neutral conditions. Building blocks prepared by this method can be rendered enantioenriched via a stereospecific sequence from chiral, nonracemic 1,3-disubstituted allylic alcohols. Future studies will involve target- and drug discovery efforts and the development of other new chemical methods inspired by these discoveries.

Scheme 11. Stereochemical Rationale: (A) Double Inversion and (B) Zimmerman–Traxler Model



EXPERIMENTAL SECTION

General Experimental Details. All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Reactions that require heating were done so on stir-heat plates using aluminum heating blocks (Pie-Blocks; ChemGlass Life Science). Anhydrous solvents were transferred via a syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran, pentane, ether, dichloromethane, and toluene were dried using a commercial solvent purification system. Anhydrous acetonitrile was dried over CaH_2 and obtained via distillation. Reaction progress was monitored by thin-layer chromatography using Analtech TLC Uniplate precoated plates and visualized by UV light, phosphomolybdic acid stain, dinitrophenylhydrazine stain, or $KMnO_4$ stain. Flash column chromatography was performed traditionally or by a Combiflash Rf+ automated flash chromatography system using a 230–400 mesh 60 Å silica gel. The eluents employed are reported as volume:volume percentages. Proton-1 nuclear magnetic resonance (^{1}H NMR) spectra were recorded by a 300, 400, 500, or 600 MHz spectrometer as indicated. Chemical shifts (δ) are reported in parts per million (ppm) downfield relative to the solvent residual peak. Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; and app, apparent. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75, 100, 125, or 150 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the carbon resonance of the solvent as indicated. Accurate mass spectra (HRMS) were obtained by the Mass Spectrometry Research and Education Center at the University of Florida and are reported as m/z (mass/charge relative ratio) with the technique indicated using an Agilent Time of Flight 6200 spectrometer. Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion.

Starting Material Synthesis. Knoevenagel adducts (alkylidene-malononitriles[36] and alkylidene Meldrum's acid adducts **8a**,[37] **8b**–**8d**[38]) were prepared by known procedures. 1,5-Dienes **1a**–**1c** and **3a**–**3c** were prepared by a standard literature procedure deconjugative alkylation.[36,39] *rac*-**6e** was prepared by a one-pot cyanohydrin formation/carbonate formation.[40] Enantiomerically enriched (>99% *ee*)-**6e** was prepared enzymatically by the known literature procedure.[33] 1,3-Disubstituted allylic electrophiles **6a**–**6d** and **6f**–**6g** were prepared by a standard literature procedure involving a Wittig reaction between an aldehyde and triphenylphosphoranylidene-2-propanone,[41] $CeCl_3$/$NaBH_4$/MeOH ketone reduction, and carbonate formation with methyl chloroformate or Boc_2O.

Wittig Reaction. To a flame-dried Schlenk flask equipped with a magnetic stir bar were added appropriate carboxaldehyde (1 equiv) and triphenylphosphoranylidene-2-propanone (1 equiv) in toluene

(0.67 M) at 100 °C under N_2. The reaction mixture was left to stir until judged complete by TLC analysis. Once the reaction was finished, toluene was evaporated from the reaction mixture and the crude material was purified by silica gel flash column chromatography (30% EtOAc:hexanes) to afford the desired α,β-unsaturated ketone.

1,2-Reduction of α,β-Unsaturated Ketones. To a round-bottom flask containing a stir bar was added the α,β-unsaturated ketone (1 equiv) in methanol (0.2 M). The reaction flask was then cooled to 0 °C in an ice bath followed by the addition of $CeCl_3$ (1.2 equiv). While the reaction mixture was still at 0 °C, $NaBH_4$ (3 equiv) was added in small portions. The reaction was then left to stir at room temperature for 1 h. Once the reaction was complete, it was diluted with water, transferred to a separatory funnel, and extracted three times with EtOAc. The organic layer was then washed with brine, dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to afford a clear oil. The crude material can be used as is for the next step.

Conversion of Allylic Alcohols to Methyl Carbonates. To a flame-dried Schlenk flask equipped with a magnetic stir bar was added the racemic secondary alcohol (1 equiv) dissolved in DCM (0.5 M) under N_2. Pyridine (2 equiv) was added, and the reaction flask was cooled to 0 °C in an ice bath before adding methyl chloroformate (2 equiv). The reaction mixture was brought back to room temperature and continued stirring until judged complete by TLC analysis. Once the reaction was complete, the contents of the flask were transferred to a separatory funnel and washed three times with H_2O. The water layer was back-extracted with DCM, and then the combined organic layers were washed with brine, dried with Na_2SO_4, and then the solvent was removed in vacuo. The crude material was then purified by silica gel flash column chromatography (15% EtOAc:hexanes) to produce the desired electrophile.

Conversion of Allylic Alcohols to tert-Butyl Carbonates. Allylic *tert*-butyl carbonate electrophiles were prepared by adding the racemic secondary alcohol (1 equiv) and 4-(dimethylamino)pyridine (DMAP, 1 mol %) in THF (0.2 M) to a flame-dried round-bottom flask equipped with a stir bar and a septum. The reaction flask was then cooled to 0 °C in an ice bath followed by the addition of di-*tert*-butyl dicarbonate (1.1 equiv). Immediately upon the addition of di-*tert*-butyl dicarbonate, a needle was placed through the septum to control the release of CO_2(g). The reaction mixture was slightly heated with a heat gun until effervescence was observed. The reaction was returned to room temperature and continued stirring until determined complete by TLC. Once the reaction was complete, THF was evaporated in vacuo and the crude material was purified by silica gel flash column chromatography.

General Procedure for the Synthesis of Products 12 and 13. *Pd-Catalyzed 1,5-Dienes Synthesis via Regioselective Deconjugative Allylic Alkylation.* Note: the below protocol began on the 0.2−1 mmol scale. A flame-dried Schlenk flask was charged with a stir bar and $Pd(PPh_3)_4$ (5 mol %). CH_2Cl_2 (0.1 M) was added via a syringe followed by Knoevenagel adduct (1 equiv), K_2CO_3 (1.5 equiv), and subsequently the allylic electrophile (1 equiv). The reaction medium was stirred at room temperature until completion as determined by TLC analysis. After reaction, the crude mixture was filtered through a pad of silica gel and concentrated in vacuo. Purification of the crude material via column chromatography (hexanes−ethyl acetate) afforded products, which were directly subjected to Cope rearrangement.

General Procedure for [3,3] Sigmatropic Rearrangement. In some cases (see Scheme 5), the Cope product was observed during the purification of the coupling reactions. In other cases, the 1,5-dienes are charged in a sealed vial and dissolved in toluene (~0.5 M), heating at 60−80 °C (specified in Scheme 5) for the indicated period of time to afford the rearranged products. Toluene was removed in vacuo, and the crude products were purified by column chromatography (hexanes−ethyl acetate) and then directly subjected to $NaBH_4$ reduction.

General Procedure for Alkylidene Reduction. $NaBH_4$ (3 equiv) was charged in a flame-dried Schlenk flask under N_2 and dissolved in MeOH/THF (1:1 ratio, 0.1 M) at 0 °C. Then, compound alkylidene Meldrum's acid (1 equiv) was added dropwise to the previous mixture at 0 °C. After completion, the reaction mixture was quenched by H_2O. The resulting solution was concentrated by rotary evaporation. The residue was purified via column chromatography (hexanes−ethyl acetate) and directly subjected to thermal (retro [2 + 2 + 2]) amidation.

General Procedure for Thermal (Retro [2 + 2 + 2]) Amidation. The reduced Cope product (1 equiv) was charged in a pressure vial and dissolved in toluene (0.1 M). The amine (or ethanol) (1 equiv) was added to the vial, and the reaction mixture was heated at 100 °C until judged complete by TLC. The reaction mixture was transferred to a separatory funnel. The contents of the separatory funnel were washed twice with 2 M HCl, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The crude material was then purified by silica gel flash column chromatography (EtOAc:hexanes) to afford the final amide product.

Example Protocol on the 1.36 mmol Scale. A flame-dried 30 mL Schlenk flask was charged with a stir bar and $Pd(PPh_3)_4$ (1 mol %, 0.136 mmol, 15 mg). Dry THF (12 mL) was added via a syringe. Alkylidene Meldrum's acid **8a** (1.36 mmol, 288 mg) was added via a syringe. The syringe was rinsed with 1 mL of dry THF. Allyl carbonate **6a** (1.1 equiv, 1.50 mmol, 361 mg) was added via a syringe. The syringe was rinsed with 1 mL of dry THF. The final concentration was 0.1 M. Cs_2CO_3 (1.5 equiv, 2.04 mmol, 663 mg) was added as a powder. The reaction was left to react until completion as monitored by TLC. After reaction, the crude mixture was filtered through a pad of silica gel and concentrated in vacuo. Purification of the crude material via column chromatography (hexanes−ethyl acetate) directly afforded the Cope rearrangement product **10a** (1.06 mmol, 400 mg, 78% yield).

12a. **Isolated**: 177 mg (>20:1 dr); **yield**: 58% over the sequence; **physical state**: yellow oil; **TLC**: R_f = 0.44 (20% EtOAc in hexanes); purified using 5% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.9 Hz, 2H), 7.50 (s, 1H), 7.34 (t, J = 7.9 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.12 (t, J = 9.0 Hz, 3H), 5.63−5.48 (m, 2H), 3.22 (t, J = 8.6 Hz, 1H), 2.42−2.31 (m, 2H), 1.86 (tdd, J = 9.5, 7.1, 4.3 Hz, 1H), 1.63−1.75 (m, 1H), 1.69 (d, J = 5.3 Hz, 3H), 1.53 (ddd, J = 10.4, 8.4, 4.3 Hz, 2H), 0.90 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.5, 143.7, 138.1, 133.4, 131.5, 129.0, 128.7, 126.3, 124.2, 119.8, 52.8, 48.1, 38.3, 28.8, 23.8, 21.4, 18.1, 16.9. **HRMS** (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}ClNO$ 370.1932; found 370.1911.

12b. **Isolated**: 30 mg (>20:1 dr); **yield:** 28% over the sequence; **physical state**: yellow oil; **TLC:** R_f = 0.32 (20% EtOAc in hexanes); purified using 15% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.52 (d, J = 7.9 Hz, 2H), 7.33 (dt, J = 13.4, 7.6 Hz, 4H), 7.21 (t, J = 6.6 Hz, 3H), 7.12 (t, J = 7.3 Hz, 1H), 7.04 (s, 1H), 5.71−5.62 (m, 1H), 5.55 (dq, J = 12.7, 6.3 Hz, 1H), 3.27 (t, J = 9.1 Hz, 1H), 2.40−2.28 (m, 2H), 1.95−1.83 (m, 1H), 1.70 (d, J = 6.1 Hz, 3H), 1.74−1.66 (m, 1H), 1.63−1.52 (m, 2H), 0.92 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.4, 145.2, 138.0, 133.8, 129.0, 128.6, 127.6, 126.0, 125.8, 124.1, 119.7, 53.4, 48.2, 38.5, 28.9, 24.0, 21.5, 21.4, 18.1, 17.0. **HRMS** (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{29}NONa$ 358.2141; found 358.2162.

12c. **Isolated**: 62 mg (>20:1 dr); **yield**: 35% over the sequence %; **physical state**: yellow oil; **TLC**: R_f = 0.55 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.17−7.01 (m, 2H), 5.66 (q, J = 6.7, 5.8 Hz, 2H), 3.73−3.48 (m, 1H), 2.49 (ddd, J = 15.2, 10.1, 5.4 Hz, 1H), 2.36 (ddd, J = 15.1, 10.3, 5.9 Hz, 1H), 1.88 (ddt, J = 12.5, 10.2, 6.4 Hz, 2H), 1.68 (d, J = 5.1 Hz, 3H), 1.64 (ddd, J = 17.1, 10.3, 6.0 Hz, 2H), 1.43 (pd, J = 6.9, 2.3 Hz, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.0, 138.0, 130.2, 129.2, 129.1, 124.4, 119.8, 45.4, 44.6, 38.3, 29.9, 29.7, 24.1, 21.6, 18.0, 15.9. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}NOF_5$ 426.1851; found 426.1871.

12d. **Isolated**: 3.1 mg (>20:1 dr); **yield:** 14% over the sequence %; **physical state**: yellow oil; **TLC**: R_f = 0.20 (50% EtOAc in hexanes); purified using 50% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 8.50 (s, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 7.8 Hz,

2H), 7.15 (d, J = 4.6 Hz, 2H), 7.10 (t, J = 6.6 Hz, 1H), 7.05 (s, 1H), 5.57 (d, J = 5.9 Hz, 2H), 3.26 (t, J = 8.1 Hz, 1H), 2.33 (t, J = 8.0 Hz, 2H), 1.90−1.80 (m, 1H), 1.69 (d, J = 3.8 Hz, 3H), 1.65−1.60 (m, 1H), 1.53−1.47 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.88−0.83 (m, 1H), 0.80 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ (ppm): 171.1, 149.7, 132.0, 129.0, 127.5, 124.1, 123.2, 119.7, 52.7, 47.6, 38.0, 29.0, 23.7, 21.3, 18.0, 17.1. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{29}N_2O$ 337.2274; found 337.2297.

12e. **Isolated**: 35.6 mg (>20:1 dr); **yield**: 14% over the sequence %; **physical state**: clear oil; **TLC:** R_f = 0.10 (20% EtOAc in hexanes); purified using 30% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.54 (d, J = 7.9 Hz, 2H), 7.48 (s, 1H), 7.33 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.00−5.81 (m, 1H), 5.37 (ddd, J = 15.2, 6.4, 2.1 Hz, 1H), 3.48−3.36 (m, 1H), 2.59−2.31 (m, 2H), 2.06−1.80 (m, 2H), 1.80−1.71 (m, 4H), 1.66−1.51 (m, 1H), 1.06−0.94 (m, 6H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 170.6, 138.0, 131.0, 130.1, 129.1, 124.9, 124.4, 124.4, 123.0, 121.0, 119.9, 119.9, 46.2, 46.0, 36.3, 36.2, 35.9, 35.7, 29.6, 24.4, 24.0, 21.4, 19.8, 19.5, 18.5, 17.9, 17.8. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O$ 285.1961; found 285.1948.

12f. **Isolated**: 62.4 mg (17:1 dr); **yield**: 24% over the sequence %; **physical state**: yellow oil; **TLC:** R_f = 0.64 (40% EtOAc in hexanes); purified using 25% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 7.51 (d, J = 7.9 Hz, 2H), 7.47 (s, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.0 Hz, 1H), 5.34 (dt, J = 20.8, 6.0 Hz, 1H), 5.19 (dd, J = 14.5, 10.3 Hz, 1H), 4.05 (bs, J = 36.4 Hz, 2H), 2.61 (dd, J = 30.8, 12.3 Hz, 2H), 2.42−2.23 (m, 2H), 1.86 (dd, J = 12.5, 8.9 Hz, 1H), 1.76−1.68 (m, 2H), 1.65 (d, J = 6.0 Hz, 3H), 1.61−1.52 (m, 2H), 1.44 (s, J = 4.7 Hz, 9H), 1.29−1.22 (m, 1H), 1.14−0.94 (m, 3H), 0.93−0.90 (m, 1H), 0.88 (d, J = 4.8 Hz, 6H).. **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ (ppm): 171.52, 154.86, 138.12, 130.99, 128.96, 127.44, 124.08, 119.67, 79.20, 50.05, 43.38, 37.89, 37.28, 30.98, 29.52, 28.48, 24.11, 20.49, 19.47, 18.07. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{42}N_2O_3Na$ 465.3088; found 465.3070.

12g. **Isolated**: 57.8 mg (>20:1 dr); **yield:** 40% over the sequence; **physical state**: pale yellow oil; **TLC**: R_f = 0.30 (30% EtOAc in hexanes); purified using 40% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 5.34 (dd, J = 15.1, 6.4 Hz, 1H), 5.20 (dd, J = 14.5, 10.7 Hz, 1H), 4.08 (bs, J = 19.5, 12.3 Hz, 2H), 3.66 (t, J = 4.6 Hz, 4H), 3.61 (t, J = 3.8 Hz, 2H), 3.43 (t, J = 4.7 Hz, 2H), 2.74−2.52 (m, 2H), 2.35−2.21 (m, 2H), 1.86 (dt, J = 10.2, 6.2 Hz, 1H), 1.79−1.70 (m, 1H), 1.64 (d, J = 6.3 Hz, 3H), 1.61−1.50 (m, 4H), 1.44 (s, 9H), 1.28−1.21 (m, J = 16.1 Hz, 2H), 1.17−0.95 (m, 2H), 0.87 (dd, J = 11.0, 6.8 Hz, 6H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ (ppm): 172.0, 154.8, 131.2, 127.3, 79.2, 66.9, 66.7, 50.1, 46.0, 43.6, 41.9, 37.3, 33.6, 28.5, 23.8, 20.5, 18.1. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{44}N_2O_4Na$ 459.3193; found 459.3187.

12h. **Isolated**: 12.5 mg (>20:1 dr); **yield**: 29% over the sequence; **physical state**: white solid; **TLC:** R_f = 0.14 (20% EtOAc in hexanes); purified using 23% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 5.36−5.26 (m, 1H), 5.21 (ddd, J = 15.2, 9.7, 1.1 Hz, 1H), 3.66 (dd, J = 6.9, 2.9 Hz, 4H), 3.60 (t, J = 5.2 Hz, 2H), 3.43 (t, J = 4.6 Hz, 2H), 2.33−2.19 (m, 2H), 1.82−1.66 (m, 5H), 1.64 (dd, J = 6.0, 1.1 Hz, 3H), 1.61−1.45 (m, 4H), 1.35−1.04 (m, 6H), 0.97−0.92 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ (ppm): 172.2, 132.1, 126.3, 67.0, 66.7, 51.0, 46.1, 43.8, 41.8, 38.9, 34.1, 32.2, 29.4, 29.1, 27.0−26.6, 24.1, 20.7, 18.6, 18.1. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{37}NO_2Na$ 358.2717; found 358.2743.

12i. **Isolated**: 14 mg (>20:1 dr); **yield:** 7% over the sequence; **physical state**: yellow oil; **TLC:** R_f = 0.13 (20% EtOAc in hexanes); **^{1}H NMR** (600 MHz, C_7D_8 at 80 °C): δ 7.41 (d, J = 7.7 Hz, 1H), 7.02−7.00 (m, 8H), 6.89−6.88 (m, 1H), 5.54 (dd, J = 15.1, 9.2 Hz, 1H), 5.34 (dq, J = 12.7, 6.3 Hz, 1H), 4.18 (d, J = 12.1 Hz, 2H), 3.16 (t, J = 8.3 Hz, 1H), 2.37−2.30 (m, 2H), 1.97−1.84 (m, 3H), 1.69 (dd, J = 13.0, 7.4 Hz, 2H), 1.58 (dd, J = 6.4, 1.3 Hz, 2H), 1.47 (s, 9H), 1.36−1.29 (m, J = 21.4, 10.0 Hz, 6H). **^{13}C{^{1}H} NMR**: see gHMBC data in the Supporting Information. **HRMS** (ESI) m/z: $[M + Na]^+$ calcd for $C_{30}H_{39}N_2O_3ClNa$ 533.2515; found 533.2515.

12j. **Isolated**: 22 mg (>20:1 dr); **yield**: 14% over the sequence %; **physical state**: yellow oil; **TLC**: R_f = 0.43 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.42 (d, J = 7.9 Hz, 2H), 7.34−7.29 (m, 5H), 7.22 (t, J = 7.4 Hz, 2H), 7.14 (t, J = 8.6 Hz, 5H), 6.76 (s, 1H), 5.69 (dd, J = 14.7, 10.0 Hz, 1H), 5.55 (dq, J = 12.9, 6.3 Hz, 1H), 3.27−3.20 (m, 1H), 2.64 (dd, J = 13.9, 6.4 Hz, 1H), 2.46 (dd, J = 13.9, 7.9 Hz, 1H), 2.27 (ddd, J = 15.4, 9.5, 5.8 Hz, 1H), 2.24−2.18 (m, 1H), 2.11 (dt, J = 14.6, 7.2 Hz, 1H), 1.94−1.87 (m, 1H), 1.75 (dd, J = 6.4, 1.0 Hz, 3H), 1.73−1.64 (m, 1H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 170.9, 142.9, 141.0, 137.8, 131.8, 130.9, 129.2, 129.0, 129.0, 128.7, 128.6, 128.5, 128.1, 127.3, 126.1, 124.2, 119.6, 51.4, 44.7, 38.3, 35.3, 29.7, 26.4, 22.7, 18.2, 14.1. **HRMS** (ESI) m/z**:** $[M + H]^+$ calcd for $C_{27}H_{28}ClNO$ 418.1932; found 418.1946.

12k. **Isolated**: 20 mg (>20:1 dr); **yield**: 17% over the sequence; **physical state**: yellow oil. **TLC:** R_f = 0.33 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50 (d, J = 7.8 Hz, 2H), 7.34 (t, J = 7.9 Hz, 2H), 7.28−7.26 (m, 2H), 7.12 (d, J = 8.2 Hz, 3H), 7.06 (s, 1H), 5.61 (dd, J = 14.7, 9.6 Hz, 1H), 5.51 (dt, J = 21.6, 6.3 Hz, 1H), 5.44 (dd, J = 17.8, 7.3 Hz, 1H), 5.32 (dd, J = 17.5, 7.2 Hz, 1H), 3.21 (t, J = 8.5 Hz, 1H), 2.46−2.39 (m, 1H), 2.30−2.23 (m, 1H), 2.08−2.02 (m, 1H), 1.94−1.91 (m, 3H), 1.87−1.80 (m, 1H), 1.70 (d, J = 5.4 Hz, 3H), 1.14−1.11 (m, 1H), 0.99 (td, J = 7.5, 2.5 Hz, 1H), 0.93 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.1, 143.0, 137.9, 133.5, 131.7, 129.2, 129.0, 128.6, 127.3, 126.2, 124.2, 119.7, 51.8, 42.7, 35.3, 28.5, 26.3, 20.8, 18.1, 14.2. **HRMS** (ESI) m/z**:** $[M + Na]^+$ calcd for $C_{25}H_{30}NOClNa$ 418.1908; found 418.1880.

12l. **Isolated**: 13.2 mg (>20:1 dr); **yield**: 17% over the sequence %; **physical state**: clear oil. **TLC**: R_f = 0.33 (10% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50 (d, J = 7.9 Hz, 2H), 7.38−7.28 (m, 2H), 7.21−7.04 (m, 2H), 5.76−5.58 (m, 2H), 5.39 (dt, J = 11.3, 7.4 Hz, 1H), 5.21 (q, J = 7.7 Hz, 1H), 3.55 (t, J = 9.8 Hz, 1H), 2.45 (ddd, J = 15.5, 10.6, 5.4 Hz, 1H), 2.32 (dtd, J = 15.2, 10.4, 9.8, 4.9 Hz, 1H), 2.12−2.06 (m, 1H), 2.05−1.98 (m, 2H), 1.96−1.79 (m, 3H), 1.72 (tq, J = 8.9, 5.7, 3.8 Hz, 1H), 1.67 (dd, J = 5.9, 1.3 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 170.9, 138.0, 133.9, 129.7, 129.4, 129.2, 125.0, 124.4, 119.8, 44.0, 39.7, 34.8, 29.9, 28.6, 27.0, 20.8, 18.0, 14.2. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{27}NOF_5$ 452.2008; found 452.2008.

12m. **Isolated**: 32.2 mg (>20:1 dr); **yield**: 28% over the sequence; **physical state**: clear oil; **TLC:** R_f = 0.30 (25% EtOAc in hexanes); purified using 30% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.50 (d, J = 7.9 Hz, 2H), 7.38−7.28 (m, 2H), 7.21−7.04 (m, 2H), 5.76−5.58 (m, 2H), 5.39 (dt, J = 11.3, 7.4 Hz, 1H), 5.21 (q, J = 7.7 Hz, 1H), 3.55 (t, J = 9.8 Hz, 1H), 2.45 (ddd, J = 15.5, 10.6, 5.4 Hz, 1H), 2.32 (dtd, J = 15.2, 10.4, 9.8, 4.9 Hz, 1H), 2.12−2.06 (m, 1H), 2.05−1.98 (m, 2H), 1.96−1.79 (m, 3H), 1.72 (tq, J = 8.9, 5.7, 3.8 Hz, 1H), 1.67 (dd, J = 5.9, 1.3 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 170.9, 138.0, 133.9, 129.7, 129.4, 129.2, 125.0, 124.4, 119.8, 44.0, 39.7, 34.8, 29.9, 28.6, 27.0, 20.8, 18.0, 14.2. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{26}N_2ONa$ 333.1943; found 333.1924.

12n. **Isolated**: 36.6 mg (>20:1 dr); **yield**: 17% over the sequence; **physical state**: brown oil; **TLC:** R_f = 0.43 (30% EtOAc in hexanes); purified using 25% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 7.51 (d, J = 7.9 Hz, 2H), 7.47 (s, 1H), 7.30 (t, J = 7.8 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H), 5.40 (dd, J = 17.5, 7.3 Hz, 1H), 5.32 (td, J = 12.7, 6.3 Hz, 1H), 5.23 (dd, J = 16.7, 7.6 Hz, 1H), 5.12 (dd, J = 14.4, 10.6 Hz, 1H), 4.05 (m, 2H), 2.69−2.56 (m, 2H), 2.47 (ddd, J = 14.8, 10.0, 5.0 Hz, 1H), 2.30−2.19 (m, 1H), 2.07−1.95 (m, 5H), 1.94−1.86 (m, 1H), 1.80−1.70 (m, 2H), 1.66 (d, J = 5.9 Hz, 3H), 1.65−1.53 (m, 4H), 1.43 (s, 9H), 1.03 (ddd, J = 23.9, 12.0, 3.3 Hz, 1H), 0.95 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ (ppm): 171.4, 154.8, 138.1, 132.9, 129.8, 129.0, 128.1, 127.6, 124.1, 119.7, 79.2, 50.6, 37.9, 36.5, 35.9, 30.5, 29.1, 28.5, 25.8, 20.9, 18.0, 14.2. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{29}H_{44}N_2O_3Na$ 491.3244; found 491.3206.

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12o. **Isolated**: 62 mg (>20:1 dr); **yield**: 50% over the sequence; **physical state**: yellow oil; **TLC:** R_f = 0.28 (50% EtOAc in hexanes); purified using 50% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28−7.25 (m, 2H), 7.13−7.08 (m, 2H), 5.64−5.40 (m, 2H), 3.69−3.56 (m, 6H), 3.34 (dd, J = 10.7, 6.0 Hz, 2H), 3.21 (t, J = 8.4 Hz, 1H), 2.36−2.19 (m, 2H), 1.73 (ddd, J = 19.1, 11.3, 5.8 Hz, 1H), 1.66 (d, J = 5.1 Hz, 3H), 1.57−1.45 (m, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 171.8, 143.7, 133.4, 131.5, 128.9, 128.6, 126.2, 66.9, 66.7, 52.7, 48.4, 46.0, 41.8, 34.3, 28.9, 23.6, 21.4, 18.1, 16.9. **HRMS** (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}ClNO_2$ 364.2038; found 364.2050.

12p. **Isolated**: 19 mg (>20:1 dr); **yield:** 60% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.14 (20% EtOAc in hexanes); purified using 20% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40−7.24 (m, 8H), 7.09 (d, J = 8.4 Hz, 2H), 5.58−5.48 (m, 2H), 4.44 (t, J = 5.7 Hz, 2H), 3.19 (t, J = 8.6 Hz, 1H), 2.28−2.19 (m, 2H), 1.83−1.75 (m, 1H), 1.66 (s, 1H), 1.64 (d, J = 5.1 Hz, 3H), 1.56−1.48 (m, 2H), 0.88 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 171.5, 143.7, 138.1, 133.4, 131.5, 129.0, 128.7, 126.3, 124.2, 119.8, 52.8, 48.1, 38.3, 28.8, 23.8, 21.4, 18.1, 16.9. **HRMS** (ESI) m/z: $[M + Na]^+$ calcd for $C_{24}H_{30}NOClNa$ 406.1914; found 406.1894.

12q. **Isolated**: 48 mg (>20:1 dr); **yield:** 59% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.14 (20% EtOAc in hexanes); purified using 30% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.28−7.24 (m, 4H), 7.09 (dd, J = 8.2, 1.6 Hz, 2H), 7.04 (td, J = 8.5, 1.7 Hz, 2H), 5.65 (s, 1H), 5.58−5.45 (m, 2H), 4.39 (d, J = 5.1 Hz, 2H), 3.19 (t, J = 8.6 Hz, 1H), 2.26−2.15 (m, 2H), 1.82−1.75 (m, 1H), 1.64 (d, J = 5.8 Hz, 3H), 1.62−1.56 (m, 1H), 1.50 (d, J = 5.6 Hz, 2H), 0.87 (d, J = 5.1 Hz, 3H), 0.76 (d, J = 5.0 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 172.8, 163.0, 161.4, 143.6, 134.3, 133.4, 131.5, 129.5 (d, J = 8.1 Hz), 128.9, 128.6, 126.2, 115.6, 115.5, 77.3, 77.1, 76.8, 52.7, 48.1, 42.8, 37.2, 28.8, 23.9, 21.4, 18.0, 16.9. **HRMS** (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}ClFNO$ 402.1999; found 402.1980.

12r. **Isolated**: 39 mg (>20:1 dr); **yield:** 39% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.38 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.64 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.13 (t, J = 10.5 Hz, 3H), 5.64−5.50 (m, 2H), 3.25 (t, J = 8.7 Hz, 1H), 2.43−2.31 (m, 2H), 1.90−1.83 (m, 1H), 1.69 (d, J = 5.3 Hz, 3H), 1.74−1.65 (m, 1H), 1.59−1.51 (m, 2H), 0.91 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.4, 143.5, 141.0, 133.2, 131.6, 128.9, 128.7, 126.5, 126.30 (q, J = 3.8 Hz), 119.2, 52.6, 48.1, 38.4, 28.9, 23.6, 21.4, 18.1, 17.0. **HRMS** (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{27}ClF_3NO$ 438.1806; found 438.1782.

12s. **Isolated**: 39 mg (>20:1 dr); **yield:** 48% over the sequence; **physical state:** yellow oil. **TLC:** R_f = 0.68 (20% EtOAc in hexanes); purified using 5% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.24−8.22 (m, 1H), 8.21 (s, 1H), 7.93 (s, 1H), 7.68 (dd, J = 8.8, 2.2 Hz, 1H), 7.28 (dd, J = 9.0, 4.7 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 5.60−5.50 (m, 2H), 3.21 (t, J = 8.4 Hz, 1H), 2.49−2.31 (m, 2H), 1.89−1.81 (m, 1H), 1.68 (d, J = 4.7 Hz, 3H), 1.72−1.63 (m, 1H), 1.58−1.49 (m, 2H), 0.89 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.5, 149.7, 146.4, 143.4, 138.0, 133.4, 131.6, 128.8, 128.7, 126.6, 126.4, 114.6, 52.9, 48.0, 38.4, 28.7, 23.5, 21.4, 18.0, 16.7. **HRMS** (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{27}N_2OCl_2$ 405.1500; found 405.1477.

12t. **Isolated**: 28 mg (>20:1 dr); **yield:** 43% over the sequence; **physical state:** yellow oil. **TLC:** R_f = 0.68 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28−7.25 (m, 2H), 7.13−7.09 (m, 2H), 5.58−5.45 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.16 (t, J = 8.9 Hz, 1H), 2.41−2.25 (m, 2H), 1.80−1.70 (m, 1H), 1.67 (d, J = 5.0 Hz, 3H), 1.61−1.58 (m, 1H), 1.53−1.47 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H).; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$): δ 173.8, 143.6, 133.5, 128.9, 128.6, 126.0, 64.2, 60.2, 53.0, 47.8, 42.5, 34.9, 28.5, 23.0, 21.4, 17.9, 16.6, 14.3. **HRMS** (DART) m/z: $[M + H]^+$ calcd for $C_{19}H_{28}ClO_2$ 323.1778; found 323.1757.

13b. **Isolated**: 113 mg (>20:1 dr); **yield:** 41% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.28 (50% EtOAc in hexanes); purified using 40% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.30 (d, J = 8.1 Hz, 2H), 7.06 (t, J = 8.0 Hz, 1H), 6.35 (d, J = 16.2 Hz, 1H), 6.18 (dd, J = 16.2, 8.1 Hz, 1H), 3.62 (d, J = 32.3 Hz, 6H), 3.47−3.39 (m, 2H), 2.59−2.52 (m, 1H), 2.43−2.35 (m, 1H), 2.33−2.27 (m, 1H), 1.93−1.84 (m, 1H), 1.74−1.65 (m, 2H), 1.23−1.19 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 171.9, 143.9, 135.2, 134.3, 128.4, 127.7, 122.9, 66.9, 66.6, 49.1, 46.0, 41.8, 39.9, 33.5, 29.2, 23.5, 21.2, 19.0, 19.0. **HRMS** (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{29}Cl_2O_2N$ 398.1648; found 398.1684.

General Procedure for the Synthesis of Products 14. *Pd-Catalyzed 1,5-Dienes Synthesis via Regioselective Deconjugative Allylic Alkylation.* Note: the below protocol began on the 0.2−1 mmol scale. A flame-dried Schlenk flask was charged with a stir bar and $Pd(PPh_3)_4$ (5 mol %). CH_2Cl_2 (0.1 M) was added via a syringe followed by Knoevenagel adduct (1 equiv), K_2CO_3 (1.5 equiv), and subsequently the allylic electrophile (1 equiv). The reaction medium was stirred at room temperature until completion as determined by TLC analysis. After reaction, the crude mixture was filtered through a pad of silica gel and concentrated in vacuo. Purification of the crude material via column chromatography (hexanes−ethyl acetate) afforded products, which were directly subjected to reductive Cope rearrangement.

General Procedure for Reductive Cope Rearrangement. 1,5-Diene (1 equiv) and Hantzsch amide (3 equiv) were charged in a pressure vial and diluted in toluene (∼0.5 M) and heated up to 120−150 °C (specified with substrate) for the indicated period of time to afford the rearranged products. Toluene was removed in vacuo, and the crude products were purified by column chromatography (hexanes−ethyl acetate) and directly subjected to oxidative esterification.

General Procedure for Oxidative Esterification. The alkylmalononitrile prepared via reductive Cope rearrangement was dissolved in MeOH (0.1 M) and cooled to 0 °C. K_2CO_3 (1.5 equiv) was then added, followed by MMPP·$6H_2O$ (1.5 equiv), and the reaction was slowly warmed to room temperature and stirred for 30 min to 1 h. The reaction was then diluted with EtOAc and washed with H_2O, brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure, and the crude material was then purified via flash column chromatography (hexanes−ethyl acetate).

14b. **Isolated**: 20 mg (>20:1 dr); **yield:** 32% over the sequence; **physical state:** clear oil. **TLC:** R_f = 0.30 (20% EtOAc in hexanes); purified using 20% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.11 (d, J = 8.0 Hz, 1H), 5.85 (dqd, J = 14.7, 6.7, 1.5 Hz, 1H), 5.64−5.44 (m, 1H), 5.38−5.18 (m, 2H), 3.49−3.33 (m, 1H), 2.58−2.29 (m, 2H), 2.29−2.11 (m, 2H), 2.10−1.93 (m, 2H), 1.92−1.80 (m, 2H), 1.79−1.75 (m, 1H), 1.74−1.71 (m, 4H), 0.97 (tt, J = 7.5, 4.2 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 173.3, 131.5, 123.5, 120.0, 52.0, 42.9, 37.7, 32.5, 28.9, 21.5, 17.8, 17.2. **HRMS** (ESI−TOF) m/z: $[M + NH_4]^+$ calcd for $C_{12}H_{23}N_2O_2$ 227.1758; found 227.1756.

14c. **Isolated**: 36 mg (>20:1 dr); **yield:** 61% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.30 (15% EtOAc in hexanes); purified using 15% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.71−5.49 (m, 1H), 5.36 (ddq, J = 15.1, 9.7, 1.7 Hz, 1H), 4.21−4.02 (m, 2H), 3.63 (s, 3H), 3.07−2.86 (m, 1H), 2.46−2.31 (m, 1H), 2.27−2.07 (m, 2H), 1.69−1.63 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 0.96−0.77 (m, 6H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 174.1, 173.8, 129.9, 127.6, 60.4, 53.7, 51.5, 42.4, 32.5, 29.6, 21.1, 17.9, 16.9, 14.2. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{25}O_4$ 257.1747; found 257.1750.

14d. **Isolated**: 19.1 mg (5:1 dr); **yield:** 39% over the sequence; **physical state**: oil; **TLC:** R_f = 0.45 (20% EtOAc in hexanes); purified using 13% EtOAc in hexanes; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) *major diastereomer*: 5.43 (dq, 1H), 5.19−4.97 (m, 1H), 4.10 (bs, 2H), 3.63 (s, 3H), 2.73−2.47 (m, 2H), 2.15 (d, J = 5.8 Hz, 2H), 2.00−1.92 (m, 1H), 1.87−1.78 (m, 1H), 1.76−1.66 (m, 2H), 1.62 (dd, J = 6.4,

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1.5 Hz, 3H), 1.44 (s, 9H), 1.30−1.13 (m, 2H), 1.12−0.95 (m, 2H), 0.88 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ (ppm): 175.0, 154.8, 130.1, 128.2, 79.2, 51.5, 50.2, 40.6, 36.9, 33.4, 28.5, 21.2, 18.0. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{37}NO_4Na$ 390.2615; found 390.2601.

14e. **Isolated**: 22 mg (>20:1 dr); **yield:** 17% over the sequence; **physical state:** yellow oil. **TLC:** R_f = 0.55 (20% EtOAc in hexanes); purified using 5% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer*: δ 7.30−7.27 (m, 2H), 7.17−7.13 (m, 2H), 5.53−5.49 (m, 2H), 5.46−5.39 (m, 1H), 5.28−5.21 (m, 1H), 3.65 (s, 3H), 3.18−3.13 (m, 1H), 2.39−2.27 (m, 3H), 1.98 (dd, J = 14.8, 6.0 Hz, 1H), 1.94−1.83 (m, 3H), 1.66 (d, J = 4.6 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 178.5, 157.1, 134.0, 132.1, 129.2, 128.6, 127.7, 127.3, 125.6, 52.7, 51.5, 40.0, 36.1, 29.4, 20.6, 18.0, 14.1. **HRMS** (DART) m/z: $[M + H]^+$ calcd for $C_{19}H_{26}ClO_2$ 321.1616; found 321.1601.

14f. **Isolated**: 29 mg (>5:1 dr); **yield:** 23% over the sequence; **physical state:** yellow oil **TLC:** R_f = 0.55 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.69−5.48 (m, 2H), 4.00 (t, J = 10.6 Hz, 0H), 3.66 (d, J = 4.9 Hz, 3H), 3.53 (dd, J = 11.3, 9.2 Hz, 1H), 2.73−2.55 (m, 1H), 2.33 (dt, J = 16.2, 4.4 Hz, 1H), 2.16 (dd, J = 16.2, 7.4 Hz, 1H), 1.72−1.59 (m, 3H), 1.55−1.37 (m, 1H), 0.92−0.65 (m, 6H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 174.2, 129.7, 129.4, 51.7, 44.4, 42.3, 33.2, 29.2, 29.0, 21.6, 21.5, 17.8, 15.6. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}O_2F_5$ 351.1378; found 351.1376.

14g. **Isolated**: 23 mg (>20:1 dr); **yield:** 27% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.45 (30% EtOAc in hexanes); purified using 20% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.62 (p, J = 3.3, 2.8 Hz, 2H), 5.39 (dtt, J = 10.6, 7.3, 1.7 Hz, 1H), 5.16 (dddd, J = 11.0, 9.1, 5.1, 1.7 Hz, 1H), 3.65 (s, 3H), 3.62−3.53 (m, 1H), 2.66−2.53 (m, 1H), 2.43 (dd, J = 16.1, 5.4 Hz, 1H), 2.39−2.27 (m, 1H), 2.05−1.78 (m, 4H), 1.69−1.60 (m, 3H), 0.95−0.80 (m, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 173.3, 134.5, 130.1, 129.0, 124.8, 51.6, 44.2, 37.6, 36.6, 29.8, 20.6, 17.9, 14.1. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}O_2F_5$ 377.1534; found 377.1521.

14h. **Isolated**: 34.4 mg (>20:1 dr); **yield:** 72% over the sequence; **physical state:** clear oil. **TLC:** R_f = 0.70 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (t, J = 5.9 Hz, 2H), 7.13 (t, J = 6.3 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 5.84−5.43 (m, 2H), 3.73−3.62 (m, 1H), 3.58 (s, 3H), 2.96−2.69 (m, 1H), 2.61−2.45 (m, 2H), 2.43−2.22 (m, 2H), 1.65 (d, J = 4.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 173.0, 139.3, 130.2, 128.9, 128.4, 126.3, 77.4, 51.6, 44.8, 39.3, 36.9, 31.7, 22.8, 17.9, 14.3. **HRMS** (ESI−TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{20}O_2F_5$ 399.1378; found 399.1378.

14i. **Isolated**: 29 mg (>20:1 dr); **yield:** 40% over the sequence; **physical state:** orange oil; **TLC:** R_f = 0.45 (30% EtOAc in hexanes); purified using 25% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.86 (dqd, J = 14.7, 6.7, 1.6 Hz, 1H), 5.58−5.47 (m, 1H), 5.42−5.21 (m, 2H), 3.68−3.46 (s, 3H), 3.55−3.46 (m, 1H), 2.51−2.29 (m, 2H), 2.27−2.12 (m, 3H), 2.10−1.99 (m, 2H), 1.79−1.68 (m, 3H), 1.01−0.92 (m, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 172.7, 135.8, 135.3, 131.5, 131.2, 124.8, 124.8, 123.2, 123.0, 119.3, 118.9, 51.9, 38.3, 38.2, 37.9, 37.4, 35.6, 35.1, 30.2, 28.2, 20.8, 17.9, 17.8, 14.3, 14.2. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{21}NO_2Na$ 258.1470; found 258.1464.

14j. **Isolated**: 17.2 mg (>20:1 dr); **yield:** 51% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.45 (15% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30 (tt, J = 6.7, 1.1 Hz, 2H), 7.25−7.13 (m, 3H), 5.89−5.39 (ddq, J = 15.2, 6.3, 1.7 Hz, 3H), 5.21 (ddq, J = 15.3, 5.3, 1.7 Hz, 0H), 3.64 (d, J = 15.1 Hz, 3H), 3.56−3.30 (m, 1H), 3.00−2.76 (m, 1H), 2.74−2.33 (m, 4H), 1.74 (ddt, J = 21.6, 6.5, 1.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 172.6, 172.4, 138.4, 138.3, 131.7, 131.2, 129.3, 129.2, 128.8, 128.7, 126.9, 126.8, 123.0, 122.7, 122.5, 119.2, 118.6, 51.9, 51.8, 39.9, 39.7, 38.8, 37.7, 37.0, 36.6, 35.3, 35.0, 17.9, 17.8. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}NO_2Na$ 280.1313; found 280.1303.

14k. **Isolated**: 16.6 mg (7:1 dr); **yield:** 31% over the sequence; **physical state:** yellow oil; **TLC:** R_f = 0.38 (20% EtOAc in hexanes); purified using 11% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) *major diastereomer*: δ 5.43−5.37 (m, 1H), 5.34 (dq, J = 14.9, 6.4 Hz, 1H), 5.26−5.19 (m, 1H), 5.12−4.97 (m, 1H), 4.08 (bs, J = 9.7 Hz, 2H), 3.64 (s, 3H), 2.62 (bs, 2H), 2.32 (dd, J = 15.2, 4.0 Hz, 1H), 2.18−2.12 (m, 1H), 2.10−1.96 (m, 6H), 1.77 (ddd, J = 9.9, 7.8, 5.4 Hz, 1H), 1.66 (dd, J = 6.4, 1.5 Hz, 3H), 1.62 (s, 1H), 1.55 (dd, J = 6.9, 1.7 Hz, 1H), 1.44 (s, 9H), 1.17−1.07 (m, 1H), 1.06−0.97 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ (ppm): 174.2, 154.8, 133.4, 129.4, 128.7, 126.5, 79.2, 51.5, 50.3, 36.7, 35.6, 35.5, 30.1, 28.5, 20.7, 18.0, 14.2. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{39}NO_4Na$ 416.2771; found 416.2751.

14l. **Isolated**: 21.4 mg (6.9:1 dr); **yield:** 43% over the sequence; **physical state:** white solid. **TLC:** R_f = 0.25 (15% EtOAc in hexanes); purified using 13% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 7.29−7.12 (m, 5H), 5.37 (dq, J = 12.8, 6.3 Hz, 1H), 5.09 (dd, J = 15.0, 10.1 Hz, 1H), 4.03 (bs, J = 47.1 Hz, 2H), 3.59 (s, J = 23.1 Hz, 3H), 2.66−2.02 (m, 6H), 1.73−1.65 (m, 4H), 1.60 (d, J = 11.7 Hz, 1H), 1.42 (s, 9H), 1.40−1.32 (m, 1H), 1.25 (s, J = 8.6 Hz, 2H), 1.01−0.84 (m, 2H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$) δ (ppm): 174.0, 154.7, 140.3, 129.2, 128.3, 126.0, 79.2, 51.5, 49.9, 39.1, 36.8, 35.2, 28.5, 18.1. **HRMS** (ESI−TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{37}NO_4Na$ 438.2615; found 438.2602.

General Procedure for the Synthesis of Products 15 and 17. **15** and **17** were prepared by analogous procedures as described above for the related malononitrile and Meldrum's acid substrates, respectively. See the Supporting Information for thermal data related to their Cope rearrangement.

16a. **Isolated**: 450 mg (>20:1 dr); **yield:** 90%; **physical state:** clear oil; **TLC:** R_f = 0.30 (20% EtOAc in hexanes); purified using 20% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.78 (ddq, J = 15.2, 6.6, 0.8 Hz, 1H), 5.25 (ddq, J = 15.2, 8.6, 1.7 Hz, 1H), 4.20−4.09 (m, 1H), 4.08−3.88 (m, 4H), 3.33 (ddt, J = 11.4, 5.6, 1.8 Hz, 1H), 3.02 (dddd, J = 14.8, 4.5, 2.6, 1.8 Hz, 1H), 2.56 (td, J = 14.4, 5.4 Hz, 1H), 2.43 (ddd, J = 14.8, 3.2, 1.9 Hz, 1H), 2.05 (ddt, J = 13.5, 5.6, 2.8 Hz, 1H), 1.96 (dd, J = 14.7, 5.6 Hz, 1H), 1.89−1.72 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 178.5, 133.9, 121.9, 118.6, 111.0, 111.0, 105.9, 87.8, 65.6, 64.9, 45.2, 37.9, 36.9, 35.8, 28.8, 17.8. **HRMS** (ESI−TOF) m/z: $[M - H]^-$ calcd for $C_{16}H_{16}N_3O_2$ 282.1248; found 282.1239.

16b. **Crude material collected**: 197.3 mg (>20:1 dr); **conversion**: >95%; **physical state**: tan solid; **TLC:** R_f = 0.24 (30% EtOAc in hexanes); material reported as is. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.29 (dq, J = 13.1, 6.4 Hz, 1H), 5.01 (dd, J = 15.1, 10.5 Hz, 1H), 4.09 (bs, 2H), 3.97−3.92 (m, 2H), 3.92−3.85 (m, 2H), 3.05 (dd, J = 11.2, 5.7 Hz, 1H), 2.79 (d, J = 14.9 Hz, 1H), 2.61 (td, J = 10.8, 2.8 Hz, 2H), 2.50 (td, J = 14.2, 5.4 Hz, 2H), 2.05 (d, J = 15.1 Hz, 1H), 2.00−1.93 (m, 1H), 1.73 (dd, J = 14.6, 5.9 Hz, 1H), 1.71−1.64 (m, 1H), 1.63 (dd, J = 13.9, 4.5 Hz, 1H), 1.59 (d, J = 6.5 Hz, 3H), 1.46 (d, J = 12.9 Hz, 1H), 1.38 (s, 9H), 1.31−1.23 (m, 2H), 1.18−1.08 (m, 1H). **^{13}C{^{1}H} NMR** (151 MHz, $CDCl_3$): δ 185.2, 154.6, 129.4, 127.3, 111.7, 111.5, 106.5, 84.4, 79.2, 65.0, 64.1, 48.8, 43.2, 36.7, 35.3, 35.1, 31.0, 28.9, 28.3, 25.4, 17.7. **HRMS** (DART) m/z: $[M + H]^+$ calcd for $C_{25}H_{36}N_3O_4$ 442.2700; found 442.2705, (DART) m/z: $[M + NH_4]^+$ calcd for $C_{25}H_{39}N_4O_4$ 459.2966; found 459.2974.

18a. **Isolated**: 90 mg (>20:1 dr); **yield:** 99%; **physical state:** yellow oil. **TLC:** R_f = 0.13 (20% EtOAc in hexanes); purified using 10% EtOAc in hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32−7.27 (m, 4H), 5.56−5.34 (m, 2H), 4.55−4.48 (m, 1H), 4.15−4.04 (m, 2H), 3.90−3.80 (m, 3H), 3.74−3.59 (m, 1H), 2.64 (td, J = 14.0, 4.6 Hz, 1H), 2.14−2.08 (m, 1H), 1.80 (s, 3H), 1.77 (s, 3H), 1.66−1.63 (m, 2H), 1.59−1.43 (m, 3H), 1.29−1.22 (m, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$): δ 181.2, 161.2, 160.9, 142.0, 132.3, 129.6, 128.9, 126.4, 117.2, 107.3, 103.9, 64.9, 64.1, 51.3, 44.1, 37.5, 36.4, 27.1, 27.0, 26.8, 18.1. **HRMS** (ESI−TOF) m/z: $[M - H]^-$ calcd for $C_{24}H_{26}ClO_6$ 445.1423; found 445.1430.

18b. **Isolated**: 16.8 mg (>20:1 dr); **yield:** 65%; **physical state:** pale yellow oil; **TLC:** R_f = 0.40 (30% EtOAc in hexanes); purified using 25% EtOAc in hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.86−5.72

(m, 1H), 5.27 (ddq, J = 15.2, 8.5, 1.6 Hz, 1H), 4.32 (dddd, J = 10.6, 5.4, 3.5, 1.7 Hz, 1H), 4.15 (dd, J = 10.6, 8.5 Hz, 1H), 4.10 (dt, J = 7.9, 6.5 Hz, 1H), 4.04 (ddd, J = 7.9, 6.5, 5.5 Hz, 1H), 3.99 (ddd, J = 7.8, 6.5, 5.5 Hz, 1H), 3.92 (dt, J = 7.7, 6.4 Hz, 1H), 3.70 (dddd, J = 13.7, 4.7, 3.0, 1.8 Hz, 1H), 2.45 (td, J = 13.7, 5.5 Hz, 1H), 2.36 (dt, J = 14.6, 3.3 Hz, 1H), 2.10 (ddt, J = 13.6, 5.7, 3.0 Hz, 1H), 1.95 (dd, J = 14.6, 5.5 Hz, 1H), 1.86 (td, J = 13.7, 4.8 Hz, 1H), 1.74 (d, J = 5.3 Hz, 6H), 1.63 (dd, J = 6.5, 1.7 Hz, 3H). **$^{13}C\{^1H\}$ NMR** (151 MHz, $CDCl_3$): δ 175.4, 160.5, 160.5, 132.2, 123.3, 119.5, 118.9, 106.9, 104.3, 65.3, 64.7, 41.5, 37.9, 37.3, 27.2, 26.4, 18.0. **HRMS** (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_6$ 379.1864; found 379.1881.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02690.

Experimental procedures, HPLC traces, thermal data for equilibrium studies related to the Cope rearrangement, ^1H and ^{13}C NMR reprints, and computational methods (PDF)

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Notes

The authors declare no competing financial interest.

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