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Article

Dramatic Effect of γ-Heteroatom Dienolate Substituents on Counterion Assisted Asymmetric Anionic Amino-Cope Reaction Cascades

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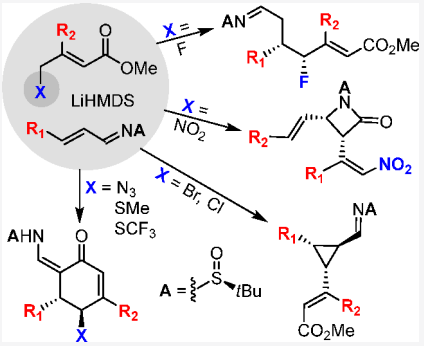
ABSTRACT: We report a dramatic effect on product outcomes of the lithium ion enabled amino-Cope-like anionic asymmetric cascade when different γ-dienolate heteroatom substituents are employed. For dienolates with azide, thiomethyl, and trifluoromethylthiol substituents, a Mannich/amino-Cope/cyclization cascade ensues to form chiral cyclohexenone products with two new stereocenters in an *anti*-relationship. For fluoride-substituted nucleophiles, a Mannich/amino-Cope cascade proceeds to afford chiral acyclic products with two new stereocenters in a *syn*-relationship. Bromide- and chloride-substituted nucleophiles appear to proceed via the same pathway as the fluoride albeit with the added twist of a *3-exo-trig* cyclization to yield chiral cyclopropane products with three stereocenters. When this same class of nucleophiles is substituted with a γ-nitro group, the Mannich-initiated cascade is now diverted to a β-lactam product instead of the amino-Cope pathway. These anionic asymmetric cascades are solvent- and counterion-dependent, with a lithium counterion being essential in combination with etheral solvents such as MTBE and CPME. By altering the geometry of the imine double bond from *E* to *Z*, the configurations at the $\mathbf{R_1}$ and **X** stereocenters are flipped. Mechanistic, computational, substituent, and counterion studies suggest that these cascades proceed via a common Mannich-product intermediate, which then proceeds via either a chair (**X** = N_3, SMe, or SCF_3) or boat-like (**X** = F, Cl, or Br) transition state to afford amino-Cope-like products or β-lactam in the case of **X** = NO_2.



INTRODUCTION

We recently reported a new asymmetric lithium-ion-mediated amino-Cope-type rearrangement for assembling chiral cyclic and acyclic products from simple building blocks.[1] This work built upon mostly overlooked earlier explorations,[2−6] whose aim was to establish an anion-accelerated amino-Cope version of Evan's seminal anion-accelerated oxy-Cope rearrangement.[7] These studies, as well as our own, revealed that the anionic amino-Cope version proceeds via a nonconcerted reaction pathway wherein the anionic Mannich adduct first fragments (retro-Mannich) followed by a recombination affording formal amino-Cope ([3,3]) or [1,3]-rearrangement products. Challenges associated with controlling the recombination step while ensuring that all retro-Mannich fragmentations proceeded productively are most likely the reasons these contributions did not become widely recognized. We postulated that these challenges could be addressed by *in situ* chelation of the two fragments with a metal counterion. We demonstrated the feasibility of this hypothesis with the productive marriage between a sulfinamide nitrogen anion, dienolate, and a lithium counterion resulting in formation of amino-Cope products with high selectivity and broad substrate scope. Our observations are particularly noteworthy when contrasted with the corresponding oxy-anion version, which when substituted with electron withdrawing groups such as esters and amides in the 4-position succumbs to the unwanted retro-aldol pathway.[8] In the context of realizing asymmetric rearrangement goals with such substrates, Schneider,[9−11] Nakai,[12] Black,[13] and Davies[14] have demonstrated that protection of the troublesome 3-hydroxyl with a silyl or benzoate group allows the oxy-Cope rearrangement to proceed albeit at very high temperatures in addition to two steps (protection/deprotection) being added to the overall synthetic sequence.

In the present study, we report on our investigations employing dienolates substituted with a heteroatom at the γ-position. We postulated that, in addition to further defining the scope and behavior of these new Cope substrates, the electron donating and withdrawing properties of the heteroatom **X**-substituents would provide invaluable insights into the

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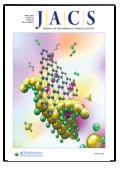


mechanism of the anionic cascade (Mannich/Cope vs Michael addition). The γ-position was chosen over the α-position, as it was postulated that (a) it would result in a less sterically congested Mannich addition step, (b) its inductive effects on the dienolate and in turn the strength of the counterion coordination would be expected to be on par with the α-position, and (c) the product would contain an additional high value second sp^3-stereocenter whose stereochemistry would afford significant clues on the transition state. Based on our earlier insights and efforts, our expectations with respect to the mechanism and anticipated stereochemical outcomes as a result of introducing γ-dienolate substituents are presented in Figure 1. Following a reversible *syn*-selective Mannich addition

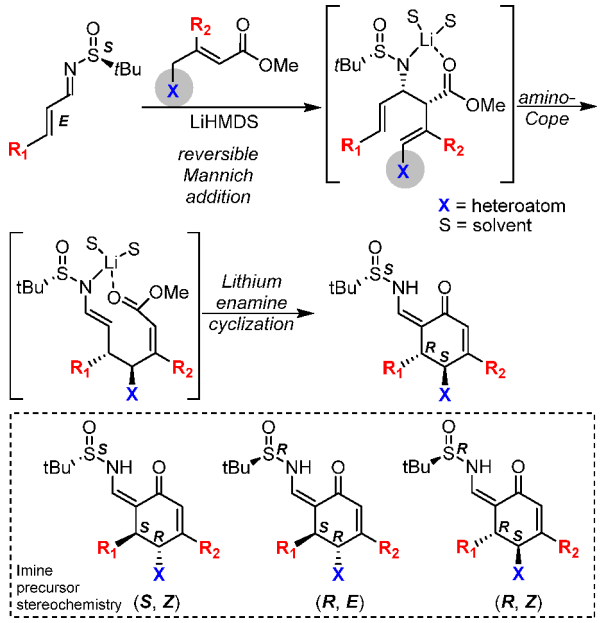


Figure 1. Proposed anionic amino-Cope studies.

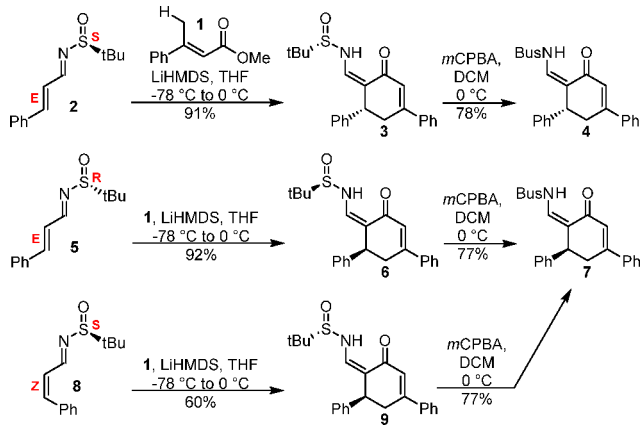
step between an *E*-conjugated Ellman-imine and a dienolate, resulting from deprotonation of γ-heteroatom-substituted propionates, a lithium guided anion-accelerated amino-Cope rearrangement would then proceed followed by a rapid enamide cyclization to form a cyclohexenone product with two new stereocenters.[15] We predicted, based on our earlier studies, that the two new stereocenters would be *anti* to each other (*R*, *S* configured at $\mathbf{R_1}$ and **X**, respectively, for an *S*-sulfinamide) in the expected product. Furthermore, it would then be expected that the three other products shown in the highlighted box could be specifically obtained by employing either *E*- or *Z*-conjugated imines in combination with the appropriately configured sulfinamide chiral auxiliary (*R* or *S*).

RESULTS AND DISCUSSION

For our debut amino-Cope studies, we utilized the esters of tiglic acid and 3,3-dimethyl acrylic acid and their trifluoromethyl variants as dienolate nucleophiles. For the present study, we opted to push the limits further in terms of the size of the nucleophile by employing 3-aryl methyl butenoates, which we postulated would provide the added benefits of providing electronic tuning by altering the nature of the 4-aryl substituent while affording more diverse and potentially higher value products.

Hydrogen (X = H). Shown in Scheme 1 are the amino-Cope results for 3-phenyl methyl butenoate (**1**) using both

Scheme 1. Anion-Accelerated Amino-Cope Rearrangement Results for 3-Phenyl Methyl Butenoate



enantiomers (**2** and **5**) of the sulfonamide auxiliary for imine electrophiles with *E*-double bonds. In both cases, the anionic Mannich-amino-Cope-cyclization cascades afford the expected chiral cyclohexenone products (**3** and **6**) in excellent yields as single stereoisomers but opposite stereochemistry. Upon oxidation of the product auxiliaries to their corresponding t-butyl sulfonamide (Bus) groups, **4** and **7** are formed, which display identical NMRs but opposite optical rotations, suggesting that this anion-accelerated amino-Cope rearrangement can be used to access either of the enantiomeric series (**4** and **7**, see Supporting Information Figure S1). The dienolate of **1** also successfully engages an imine with a **Z**-double bond (**8**), albeit in a bit lower yields, to deliver **9** which following sulfonamide oxidation is shown to be identical in all respects to **7**.

With the viability of the new 3-aryl-substituted nucleophile established, we turned our attention to investigating 3-aryl methyl butenoates containing heteroatom substituents in the γ-position.

Azide (X = N_3). Given the important role nitrogen atoms play as essential components of the majority of approved pharmaceuticals[16,17] and countless natural product structures, we initiated our heteroatom substituent studies by identifying a suitable nitrogen atom functional group. It quickly became evident to us that azides represented an excellent nitrogen atom representative for our studies.[18] Azides are not only one of the smallest nitrogen atom substituents as well as a versatile functional group handle for further manipulations, but their unique structure helps avoid any unwanted nucleophilic or basic behavior of many typical nitrogen atom substituents. Furthermore, for our purposes, the γ-substituted azide 3-aryl butenoates that we required for our studies would be easy to synthesize and stable as a result of electronic deactivation by enoate and a relatively high carbon atom count.

We were delighted to learn that when azide-containing enoate **10** was treated with lithium bis(silyltrimethyl)amide (LiHMDS) in the presence of chiral sulfiname imine **11** the expected anionic amino-Cope cascade ensued to afford a chiral cyclohexenone product **12** in very good yield as a single stereoisomer. For this cascade, methyl *t*-butyl ether (MTBE) was shown to afford the product in higher yield compared to tetrahydrofuran (THF). Proving the stereochemistry at the

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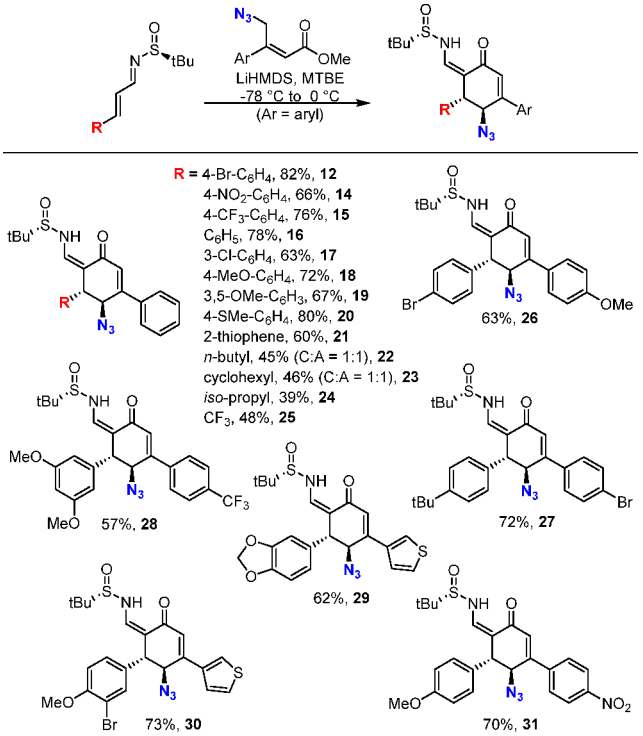
newly formed stereocenter proved to be challenging using NMR, as coupling constants between the C−H's of the adjacent stereocenters were not deemed reliable. This assignment was confidently confirmed following treatment of the sulfinamide group with an oxidant (m-CPBA) to deliver a crystalline sulfonamide product, thereby allowing single crystal X-ray analysis and confirmation of an *anti*-relationship between the two sp^3-stereocenters. Absolute configuration was assumed based on crystal structures lacking the azide group obtained in our earlier studies. Crystal structure reveals that the azide and the adjacent aryl group both adopt axial positions, thus accounting for the surprising coupling constants observed in the proton NMR spectra.

We have evaluated this new Mannich-amino-Cope-cyclization cascade for a series of imines and dienolates (Table 1).

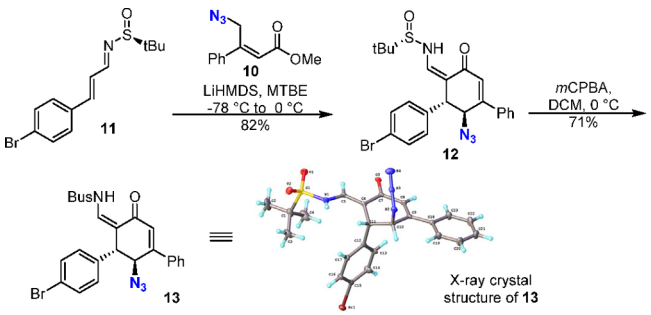
Table 1. Amino-Cope Cascade Scope with Azide Nucleophiles



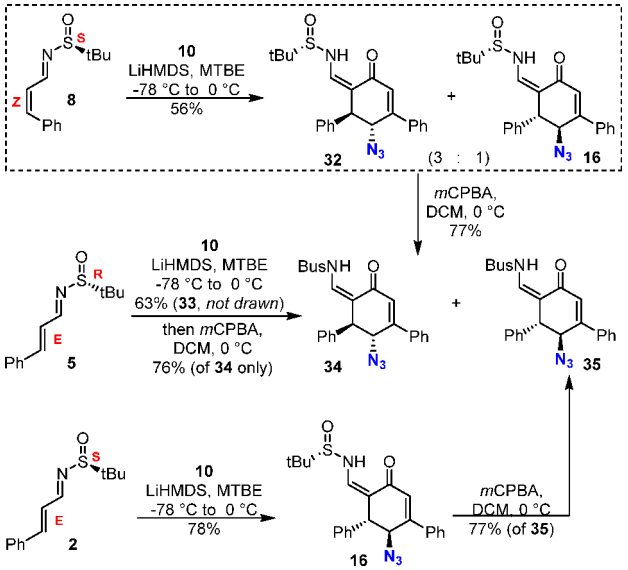
Yields are generally very good with higher yields observed for imines with aromatic compared to alkyl substituents, which is consistent with observations we made in our first report. Interestingly, for alkyl substrates **22** (*n*-butyl) and **23** (cyclohexyl), an acyclic amino-Cope product is obtained with an *E*-configured double bond and *syn*-configuration between the newly formed stereocenters.

We next evaluated if a *Z*-imine would be compatible with our asymmetric cascade (Scheme 3). Treatment of *Z*-imine **8** with azide nucleophile **10** revealed that a *Z*-imine is indeed compatible, affording two cyclized products **32** and **16** in a 3:1 ratio and good yield, albeit lower yield than the corresponding *E*-imine. We predicted that cyclohexenone **32**, with opposite stereochemistry of the newly formed stereocenters to that obtained from *E*-imines, but leaving no stones unturned, we decided to confirm this assignment unambiguously. This was accomplished by treating *E*-imines **5** and **2**, which only differ in the absolute stereochemistry of the sulfinamide chiral auxiliary,

Scheme 2. γ-Azide-Substituted Butenoates Are Successful Nucleophile Partners for the Anionic Amino-Cope Cascade



Scheme 3. *Z*-Imines Engage Azide Nucleophile



with our optimized amino-Cope cascade reaction conditions followed by oxidation of the auxiliary to a t-butyl sulfonamide (Bus) group. These studies revealed that our structural assignment of **32** was indeed correct and that the minor product (**16**) was the other *anti*-product matching the oxidized product originating from an amino-Cope cascade originating from *E*-imine **2**.

We next turned our attention to evaluating the compatibility of sulfur substituents for the anionic cascade. Following the four key elements of life (C, H, O, and N), which account for the structural bulk and architectural frameworks of US FDA approved pharmaceuticals, it is sulfur (S) which reigns supreme as the fifth most commonly occurring element in drugs.[19]

Thiomethyl (X = SCH_3). We were pleased to learn that, when we employed dienolate nucleophiles substituted with a γ-thiomethyl group (**36**), the same novel Mannich-amino-Cope-cyclization cascade we had observed for azides ensued (Table 2). Yields are very good for aromatic substituents (R and Ar), and as with other series, the yield drops a bit when alkyl (R) substituents are used. Using cyclopentyl methyl ether (CPME) as the solvent, we observed improved yields compared to THF and MTBE. Unlike the azide series, the thiomethyl substituent affords two amino-Cope products, which we have named cyclic (C, cyclization following the amino-Cope step) and acyclic (A). The structures of these products do not only differ in their enoate double bond geometry, with a *Z*-enoate for the cyclic

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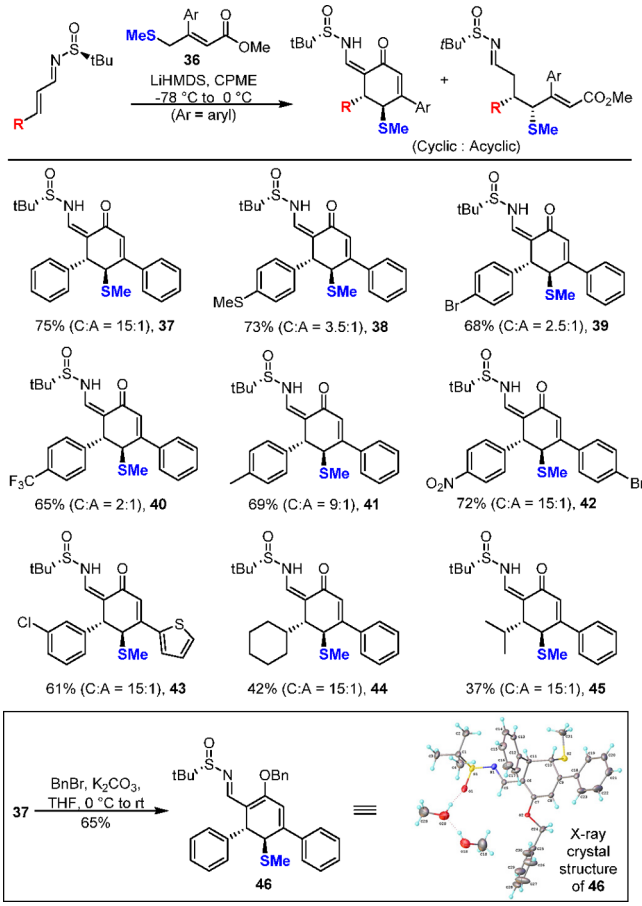
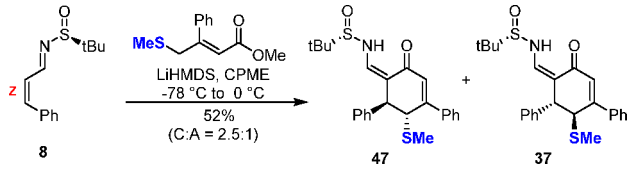
Table 2. Amino-Cope Cascade with Thiomethyl Nucleophiles



product and an *E*-enoate for the acyclic product, but the newly formed stereocenters have a *syn*-relationship in case of acyclic product compared to the *anti*-relationship for the cyclic product. In all cases, the cyclic product is the major product, and overwhelmingly so for most substrates. We were able to convert one of the products (**37**) into imine enol ether product **46** under mild O-alkylation reaction conditions. Most gratifyingly, enol ether **46** was crystalline, which allowed us to secure a single X-ray crystal structure of it and therefore to unambiguously determine the relative and absolute stereochemistry of the cyclic product series and confirm that its structure matched our observation for the azide nucleophiles. It is noteworthy to mention that the starting double bond geometry of the enoate does not seem to influence the outcome as azide nucleophile **10** (*Z*-double bond) and thiomethyl nucleophile **36** (*E*-double bond) both result in cyclic products with the same relative and absolute configuration.

We next evaluated the compatibility of *Z*-imines as partners in the anionic cascade with a thiomethyl nucleophile (Scheme 4). Reaction between *Z*-imine **8** and thiomethyl-substituted dienolate shown under our standard reaction conditions afforded two cyclized products **47** and **37** in a 2.5:1 ratio, albeit in lower yield than the corresponding *E*-imine. This result is similar to what we observed with the azide substitution (Scheme 3, top part). Substrate **47** also has the *anti*-stereochemistry at the aryl- and thiomethyl stereochemistry but opposite configuration to those originating from *E*-imines.

Scheme 4. *Z*-Imine Reacts with Thiomethyl Nucleophile

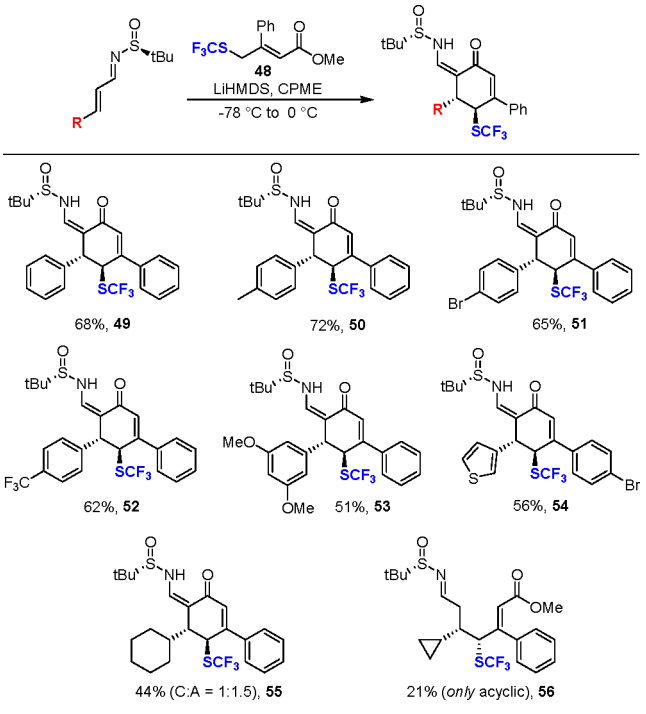


This powerful feature of these new asymmetric anionic cascades enables access to either *anti*-configuration of the product from a single chiral auxiliary by simple choice of *E*- or *Z*-imine reaction partners.

Following the success of the thiomethyl nucelophiles, we next decided to further probe the impact of electronics of the sulfur substituent by replacing the methyl group with a trifluoromethyl group, which would minimally alter the size of the nucleophile while significantly impacting dienolate electron density. It is worth mentioning that the trifluoromethyl thiol group (SCF_3) possesses attractive physicochemical properties such as high lipophilicity (Hansch parameter $\Pi = 1.44$).[20] As such, this moiety continues to receive interest in disciplines such as medicinal chemistry and agrochemistry.[21] Therefore, novel trifluoromethylthiolation strategies, in particular asymmetric, continue to be of interest.

Trifluoromethylthiol (X = SCF_3). The results of our fluorine inductive effect studies with trifluoromethylthiol-substituted nucleophile **48** are reported in Table 3. First, this

Table 3. Trifluoromethylthiol Nucleophiles



nucleophile is indeed compatible with the Mannich-amino-Cope-cyclization cascade affording expected cyclized products in fair to good yields and as single stereoisomers with the *anti*-relationship between newly formed stereocenters as observed for azides and thiomethyl-substituted nucleophiles. Interestingly, and in a slight contrast to the thiomethyl nucleophiles, all of the products with an aromatic imine substituent proceeded to cyclize with no observed acyclic products. The exception to

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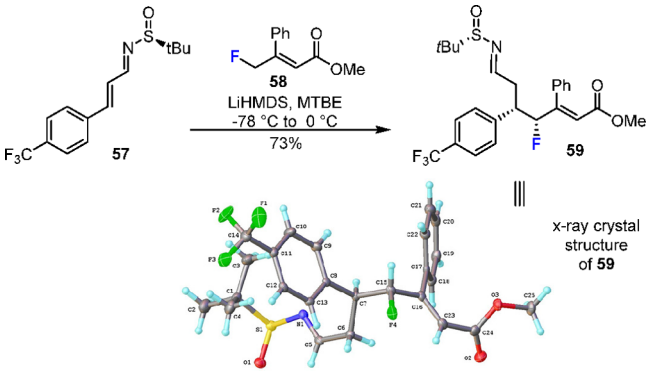
this was when alkyl substituents (cyclohexyl and cyclopropyl, **55** and **56**) were employed, where we observed the acyclic product as the major component for the cyclohexyl substituent or as the sole product in the case of cyclopropyl.

It is fair to say that fluorine has taken the pharmaceutical[22] and agrochemical industries by storm, as is evident from the large number and continued increase of approved small molecules containing fluorine atoms in the last two decades. This is not entirely surprising given fluorine's small size (not much larger than hydrogen) while packing a punch with respect to electronic impact, strong C−F bond, and a multitude of other attractive attributes.[23,24] We decided to next explore the behavior and compatibility of fluorine-substituted nucleophiles.

Fluoro (X = F). When we subjected imine **57** to the dienolate nucleophile resulting from deprotonation of γ-fluoro-substituted enoate **58**, a new product (**59**, Scheme 5) was

Scheme 5. Fluorine-Substituted Nucleophile Participates in the Amino-Cope Cascade

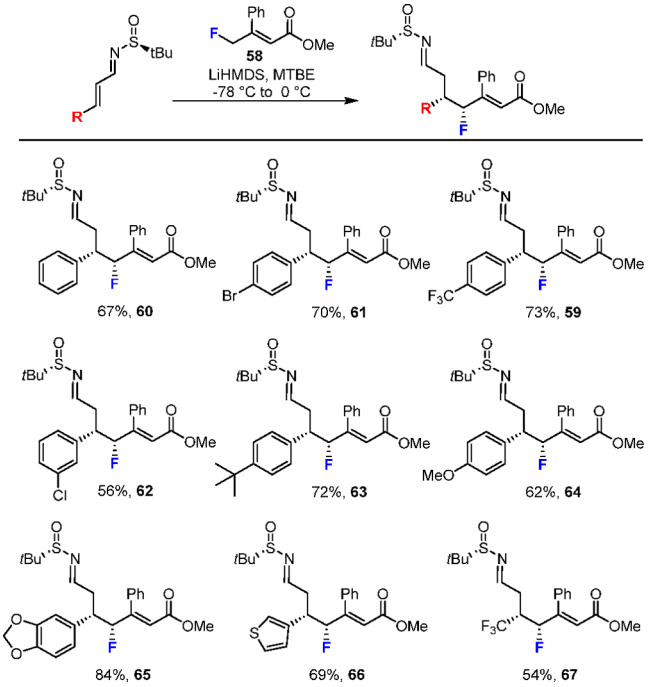


formed. Initial NMR analysis of compound **59** suggested an acyclic product similar to what we had observed in the thiomethyl series (Table 2). Fortunately, we were able to grow crystals of this new product and in turn secure a single X-ray crystal structure analysis, which revealed not only that the product was acyclic with an *E*-enoate double bond but that the newly formed stereocenters had a *syn*-relationship (not *anti* as in the azide, thiomethyl, and trifluoromethylthio series). More importantly, with the chiral auxiliary still in place, this crystal structure allowed us to unequivocally confirm both the absolute and relative stereochemistry of **59**.

We have proceeded to further evaluate how other imine electrophiles behave when treated with fluorine-substituted nucleophile **58** (Table 4). The imines we have evaluated to date all proceeded to undergo a Mannich-amino-Cope cascade and afford acyclic products with a *syn*-stereochemical relationship between the fluorine and imine substituents. Yields are mostly very good with MTBE being shown to be the most suitable ethereal solvent. The highly fluorinated product **67**, which originated from a cascade employing a trifluoromethyl-substituted imine, is particularly noteworthy.

Not surprisingly, given the unexpected outcome that the fluorinated nucleophile exhibited compared to the other heteroatom substituents explored, we decided to explore other halogen substituents to learn if they followed the same reaction pathway as fluorine. In this regard, we were most intrigued in exploring the behavior of chlorinated nucleophiles. This was inspired by a recent pharmaceutical structural analysis

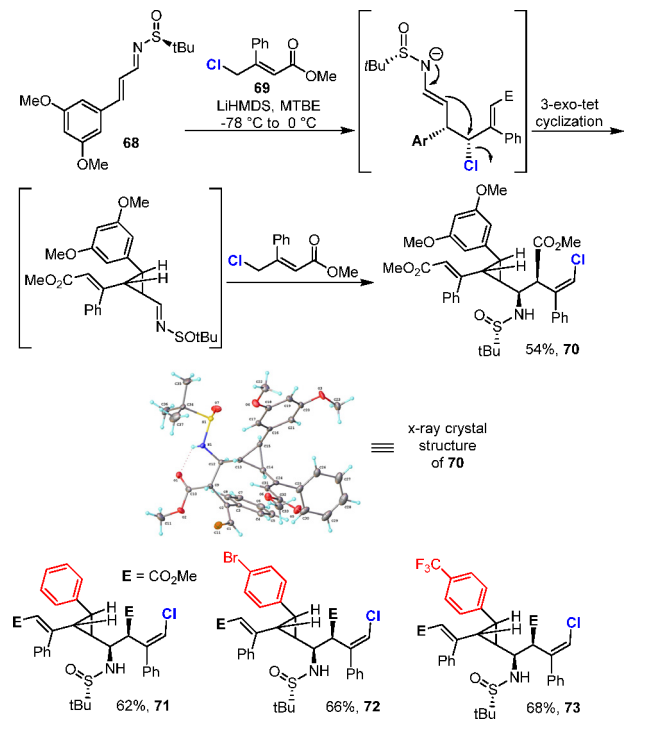
Table 4. Amino-Cope Cascade with Fluorinated Nucleophile



we conducted,[25] wherein it was revealed that as of recently there were more approved drugs containing a chlorine atom than fluorinated ones, with only a handful being decorated with either a bromine or iodine atom.

Chloro and Bromo (X = Cl and Br). We proceeded to evaluate the nucleophilic addition behavior of the dienolate originating from γ-chloro enoate **69** (Scheme 6). Treatment of

Scheme 6. Chlorine-Substituted Nucleophile Participates in the Amino-Cope Cascade, Forming Cyclopropane Products



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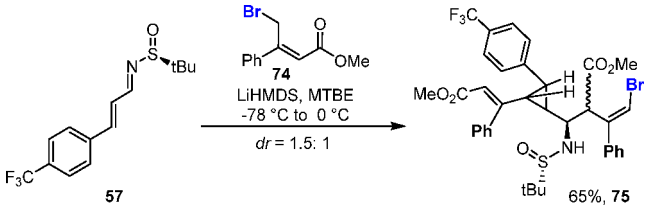
69 in the presence of imine **68** and MTBE as solvent resulted in a rapid anionic cascade, which produced a more complex proton NMR spectra than we had expected, including the presence of two methyl ester groups as well as a chlorine atom attached to a double bond. Close inspection of the NMR spectra soon revealed the presence of a cyclopropane group, resulting from intramolecular 3-*exo-tet* cyclization of the *in situ*-formed enamide resulting from initial Mannich-amino-Cope (or Michael addition) steps. Remarkably, the cyclopropane imine could not be isolated, as second addition of a dienolate nucleophile proved to be faster than addition to the starting imine, thus affording **70** as the product. This outcome is quite a contrast with the fluorine nucleophile addition results, wherein no second addition of a dienolate nucleophile was observed. With such a complex product, containing five contiguous sp^3-stereocenters as well as two double bond stereoisomers, we were not confident relying on NMR for satisfactory structural analysis. Fortunately, after much experimentation, we were finally successful in growing crystals of **70** that allowed us to secure a single X-ray crystal structure and thus enabling definite confirmation of its structure as well as its absolute and relative stereochemical assignments. Most importantly, working backward based on the stereochemistry of the cyclopropane, we were able to deduce that the chlorinated dienolate nucleophile followed exactly in the footsteps of the fluorinated nucleophile to afford an acyclic product with a *syn*-relationship between the two new stereocenters as well as an *E*-enoate double bond. We have evaluated this amazing Mannich-amino-Cope-cyclization-Mannich anionic cascade that also proceeded for additional imines, all of which afforded similar products (**71**−**73**) in very good yields. We were also able to isolate the mono addition imine product (see Supporting Information Scheme S3) for the R = 4-$CF_3C_6H_4$ substituent.

With chlorine nucleophile results firmly established, we turned our attention to evaluating the addition and anionic cascade behavior of γ-bromo enoate **74** (Scheme 7). The

Scheme 7. Bromine-Substituted Nucleophile Is Also Competent for the Amino-Cope Cascade

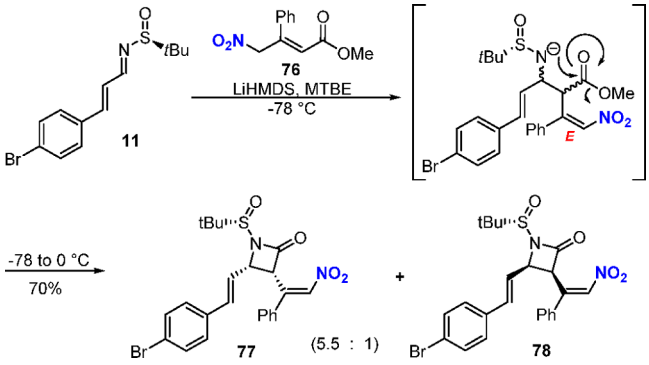


dienolate of this enoate progressed to follow the exact same multistep anionic cascade that the chloride nucleophile had established. In the bromo case, there was a small deviation in outcome as two diastereomeric products were isolated (**75**), differing only in their stereochemistry at the ester sp^3-stereocenter. This could be a result of the less selective second addition step or post-epimerization following addition.

We also evaluated an iodo-substituted nucleophile and learned it did afford the expected cyclopropane product albeit in very low yield (less than 10%), which we tentatively attribute to its larger atomic size compared to the other halogens. With the halogens behaving differently to azide, thiomethyl, and trifluoromethylthiol groups, we decided to explore how extremes in terms of γ-nucleophile substituent electronics and size impacted imine additions and ensuing anionic cascades.

Nitro (X = NO_2). We chose a nitro group as a great γ-substituent that would strongly influence the electronics of the dienolate nucleophile, while also delivering a versatile nitrogen atom substituent for post-cascade applications. Toward that end, we synthesized nitro-substituted enoate **76** and subjected it under our standard reaction conditions to imine **11**. The reaction proceeded to form two products in a 5.5:1 ratio, which NMR revealed still contained three olefinic protons and absence of a methyl ester signal (Scheme 8). Further 1D and

Scheme 8. Nitro-Substituted Nucleophile Diverts the Path toward β-Lactam Formation



2D NMR, especially NOE analyses, soon uncovered that these new products were indeed diastereomeric divinyl β-lactams (**77** and **78**) differing only in their *syn*-relationship of the vinyl substituents.

The complete *syn*-selectivity and moderate diastereoselectivity (5.5:1) are strikingly similar to what we observed in a recent vinylogous *aza*-Darzens vinyl aziridine study[26] wherein it was established that a competing retro-Mannich pathway accompanied by imine isomerization was responsible for low diastereoselectivity. Close inspection of Hammett and modified Swain−Lupton constants[27] reveals a much higher σ_p value for a nitro group compared to that of F, Cl, Br, N_3, SMe, and SCF_3 may help explain why a strong electron withdrawing group could suppress the amino-Cope pathway from opening the door for β-lactam formation. We hypothesize that not only the double bond geometry of the nitro olefin adds in concert a steric burden on the amino-Cope transition state but the presence of such a strong electron withdrawing group also increases the electrophilicity of the adjacent double bond carbon which destabilizes the amino-Cope transition state and leads to a β-lactam pathway. Alternatively, it is also possible that β-lactam formation occurs via the intermediacy of a ketene intermediate.

To help shed additional light on how the Mannich addition step and resulting amino-Cope or β-lactam cascades are impacted by γ-nucleophile substituents, we decided to explore more electron donating substituents represented by methyl and methoxy groups.

Methyl (X = CH_3). Deprotonation of methyl-substituted enoate **79b** in the presence of imine **57** only afforded Mannich product **80** with the R = CF_3 group (Scheme 9). Importantly, this Mannich product **80** does not undergo either an amino-Cope reaction or a β-lactam formation but instead readily undergoes an isomerization to the most-substituted Mannich product when resubjected to base (LiHMDS). However, when

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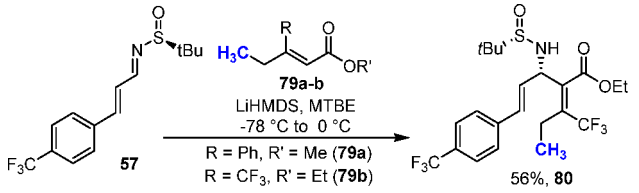
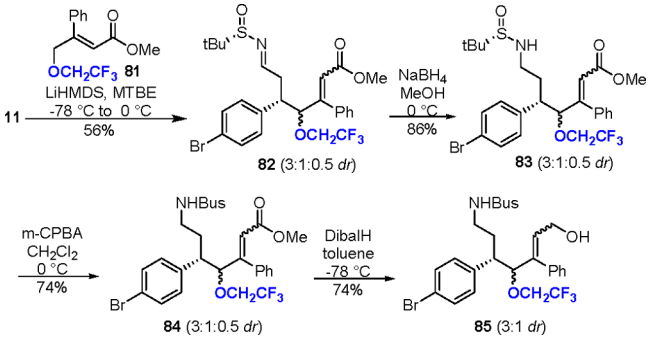
Scheme 9. Methyl-Substituted Nucleophile Undergoes Mannich/Isomerization



R = Ph (**79a**), a Mannich adduct was noticed, but over time, it underwent a retro-Mannich reaction.

Trifluoroethoxy (X = OCH_2CF_3). We next evaluated the dienolate originating from deprotonation of trifluoroethoxy (**X** = OCH_2CF_3)-substituted enoate **81** (Scheme 10). When

Scheme 10. Dienolate of the Trifluoroethoxy Substituent Adds Unselectively to Imine



reacted with imine **11**, a slow reaction ensued, which seemed to mostly form a Mannich adduct but over time produced a new product (**82**) as a nonselective 3:1:0.5 mixture of three diastereomers. This mixture could have arisen from either a Mannich-amino-Cope cascade or a direct Michael addition. We were curious to learn more about this structure, which we pursued through a series of degradation experiments. These experiments revealed that the imine was the same in all structures and the auxiliary had not been compromised, leading us to postulate that the newly formed methoxy stereocenter and the ester double bond geometry were most likely responsible for this mixture.

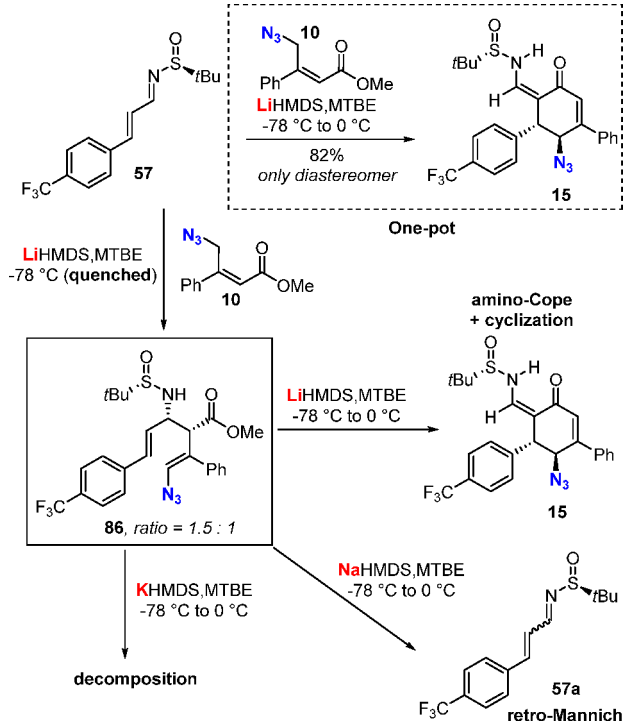
Similarly, when we employed a methoxy (**X** = OCH_3)-substituted nucleophile (not shown, see Supporting Information Scheme S5), we observed the same product as in the trifluoroethoxy case but in lower yield (32%) and as a mixture of three diastereomers in the ratio of 2:1:1.

MECHANISTIC INVESTIGATIONS

We were curious to learn how the change in counterion would affect these γ-substituted asymmetric amino-Cope reaction cascades. We performed counterion studies with isolated Mannich adduct **86** (generated by quenching the reaction at −78 °C) and resubjected it to alternative bases (LiHMDS, NaHMDS, and KHMDS). It is important to note that the initial Mannich reaction proceeded to form a mixture of two products in a 1.5:1 ratio with *E* and *Z* at the ester sp^3-stereocenter. Our preliminary investigations have revealed that the Li counterion was critical for the success of the rearrangement while Na and K were detrimental. This suggests that the Li counterions are playing a key role, most likely by suppressing the dissociations that plagued earlier investigations. This interesting reaction outcome has allowed us to confirm that both Mannich products undergo a retro-Mannich reaction to form lithium dienolate and sulfinylimine but only the matched lithium dienolate recombines with sulfinylimine to form the desired cylcohexenone product as the only diastereomer.

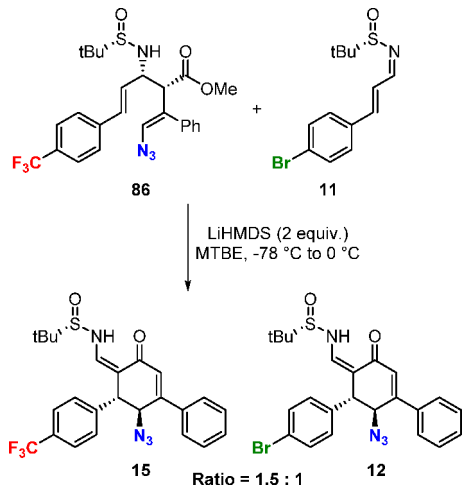
To further understand the aforementioned lithium chelation effects and the significance of the retro-Mannich pathway, the isolated Mannich adduct **86** was subjected to a competition experiment with excess 4-Br-phenyl imine **11** and LiHMDS. In this case, both the chiral cyclohexanones **15** and **12** were formed in the ratio 1.5:1 (Scheme 12). Taken together, these

Scheme 11. Counterion Effects



results suggest that the favored mechanism is indeed a stepwise dissociative one. Upon treatment with excess base, adduct **86**

Scheme 12. Mannich Crossover Experiment



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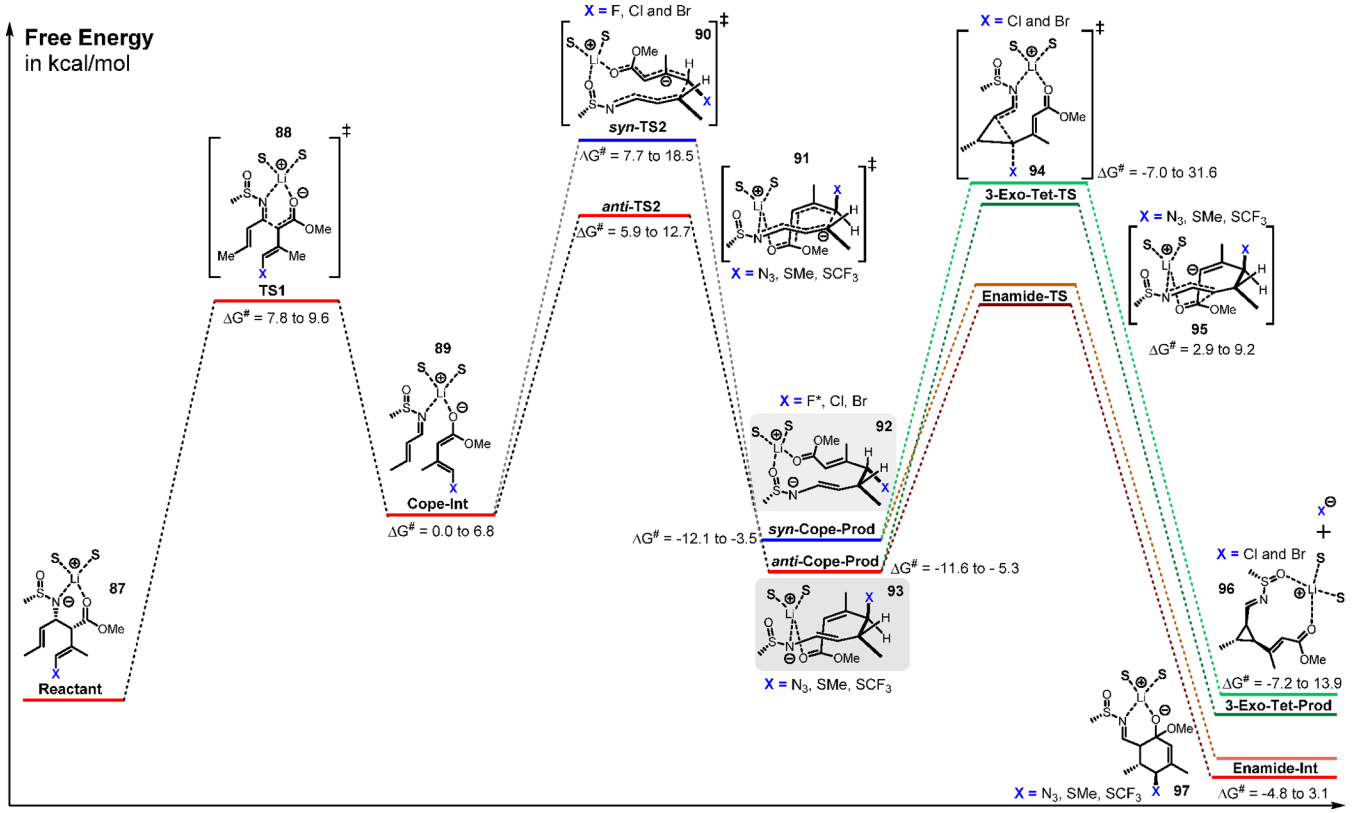
Scheme 13. Free Energy Diagram for the γ-Substituted Asymmetric Amino-Cope Reaction Cascades[a]



[a]**S** = solvent, i.e., THF. * means when **X** = F (fluorine), the reaction stopped at acyclic imine with a *Z* double bond at the ester moiety. **X** = N_3, SMe, SCF_3, F, Cl, and Br unless otherwise stated. The DFT-calculated energies for each species for each substrate are tabulated in Table 5.

Table 5. DFT-Calculated Energies for Each Species of the Rearrangement Mechanism for Each Substrate[a]

reactant	TS1	Cope-Int	*anti*-TS2	*syn*-TS2	*anti*-Cope-Prod	*syn*-Cope-Prod	3-Exo-Tet-TS	Enamide-TS	3-Exo-Tet-Prod	Enamide-Int	Enamide-Prod
When X = N_3, SMe, SCF_3											
when **X** = N_3	8.0	0.0	5.9	13.6	**−10.9**	−8.4	15.9	2.9	−3.8	−2.6	26.3
when **X** = SMe	9.6	1.5	11.3	18.5	**−5.3**	−3.5	31.6	9.2	13.9	3.1	29.2
when **X** = SCF_3	8.6	0.2	8.6	15.9	**−6.6**	−6.0	14.4	8.3	−10.6	2.3	31.6
When X = F, Cl, Br											
when **X** = F	8.9	6.8	10.6	9.1	−11.6	**−12.1**	26.4	5.5	11.0	−4.5	25.3
when **X** = Cl, Br	7.8	2.3	12.7	7.7	−9.2	**−10.6**	7.0	6.6	−7.2	−4.8	24.9

[a]Energies are given in kcal mol^{-1}.

undergoes a retro-Mannich reaction, which is then followed by a Li-chelation assisted Mannich recombination of the lithium dienolate with both sulfinylimines. These fragments recombine in the desired chair transition state, resulting in the formation of *anti*-Cope products **15** and **12** as single diastereomers. In other words, the lithium chelation assisted amino-Cope step serves as the gatekeeper that allows the amino-Cope reaction to proceed (matched case) or to be rejected (mismatched case) via a retro-Mannich step (see Supporting Information Figures S4−S6).

■ COMPUTATIONAL RESULTS AND DISCUSSION

Density functional theory (DFT) with the M06-2X functional and 6-311+G(d,p) basis set was employed to shed further light on the mechanism of the new amino-Cope rearrangement cascades (Scheme 13). The DFT-calculated energies for each species of the rearrangement mechanism for each intermediate and substrate are detailed in Table 5. The model truncates the *tert*-butyl group of the sulfonamide to a methyl, and a lithium counterion with two explicit THF solvent molecules are coordinating to the anionic structure.[28] (See the Supporting Information for full details on the computational methods.)

As we have previously discussed, the favored mechanism is a stepwise dissociative mechanism.[1] The first step TS1 **88** in the rearrangement mechanism is the cleavage of the C_3−C_4 to form a lithium dienolate and sulfinylimine that coordinate to the lithium counterion Cope-Int **89**. These fragments recombine in a chair transition state (TS2) to form the new carbon−carbon bond between C_1−C_6, which we calculate to have a slightly higher energy than TS1. These fragments recombine to form either the *syn*- or *anti*-Cope product (**92** and **93**). The formation of the Cope products is calculated to be exergonic for both product isomers for all substitutions. Subsequently, after the formation of the Cope product, each substrate continues to rearrange either through (1) an

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intramolecular S_N2-like transition state between C_2-C_6-X 3-*exo-tet*-TS **94** to form a cyclopropane ring 3-*exo-tet*-Prod **96** or (2) C_2-C(ester) Enamide-TS **95** to form a six-membered ring intermediate Enamide-Int **97** that quickly releases a methoxy anion to generate cyclohexanone products.

The relative configuration of the neutral sulfinylimine has a lasting impact on what stereoisomeric products are available. The sulfinylimine fragment within the intermediate complex Cope-Int **89** contains two single bonds that can potentially rotate around to generate sets of unique conformers. One set can be either *s-cis* or *s-trans* around the internal single bond, and one set can position the lone pairs of the N and S of the sulfonamide can either be *syn* or *anti* (see Supporting Information Figure S7). Our modeling suggests that the *s-trans* conformer is more stable by 2.8 kcal mol^{-1}, and just as in our previous study,[2] the lone pairs of the N and S atoms are more stable in the *anti*-conformation by 2.5 kcal mol^{-1}.[29] This fragment is prevented from complete free rotation due to steric clashes with the methyl group of the sulfonamide and the surrounding THF molecules and methyl ester group on the enolate fragment. These preferences combined with limited rotational freedom of the sulfinylimine to completely rotate within the intermediate complex ensure that the *re*-face of this fragment is the only face open for the recombination step (TS2 **90** and **91**).

We first investigated the full rearrangement mechanism for the N_3/SMe/SCF_3 substrates. These substrates preferentially form the *anti*-Cope product **93** and further cascade to form the enamide species. The *anti*- and *syn*-**TS2** for the N_3-substrate is shown in Figure 2. The *anti*-TS2 is 7.7 kcal mol^{-1} lower in

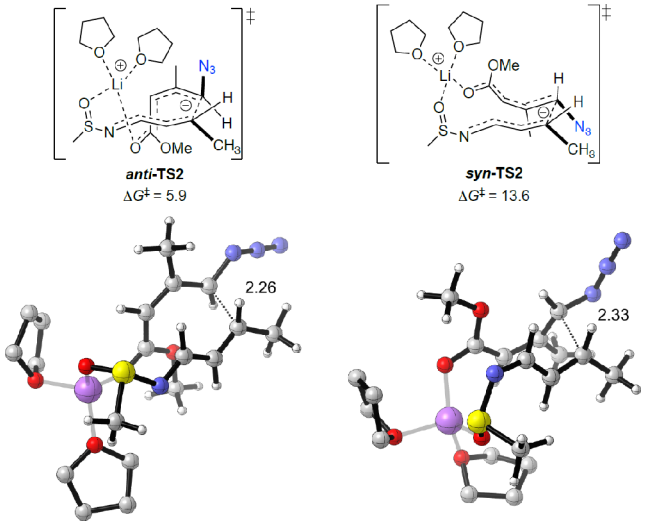

Figure 2. DFT-calculated structures of γ-N_3-substituents.

energy than the *syn*-TS2, and the *anti*-Cope-Prod is 0.6–2.5 kcal mol^{-1} lower in energy than the *syn*-Cope-Prod. Each of these substrates has the capacity to form the **3-exo-tet** and enamide products, yet the enamide product is exclusively observed. We find that the barrier to form the enamide is much lower in energy than the barrier to form the 3-*exo-tet* TS by nearly 9–22 kcal mol^{-1}, respectively, due to the ring strain associated with the formation of a cyclopropane ring and poor leaving group formation. At cryogenic temperatures, the formation of the kinetic product (enamide) is favored even though the energy of forming the Enamide-Int **97** is less favorable than that of the 3-*exo-tet*-Prod **96**.

We next investigate the full rearrangement for the fluoro-substrate. This substrate forms the *syn*-Cope-Prod **92** and does not further cascade into either the 3-Exo-Tet-Prod or enamide product (Enamide-Int). The calculated energy for the *syn*-TS2 is 1.5 kcal mol^{-1} lower in energy than the respective *anti*-TS2 (Figure 3), and the calculated energy for the *syn*-Cope-Prod is

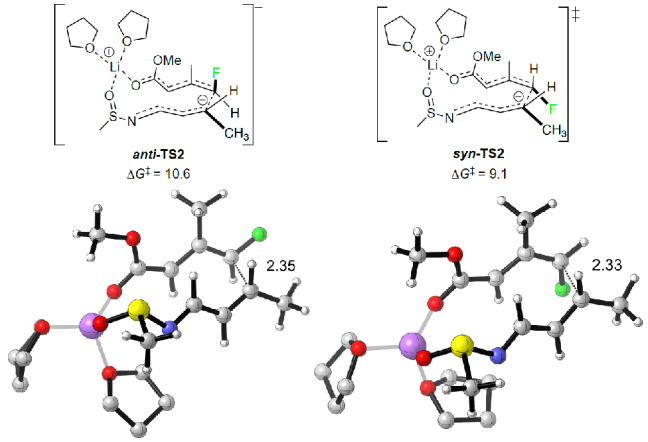

Figure 3. DFT-calculated structures of γ-F-substituents.

0.5 kcal mol^{-1} lower in energy than the respective *anti*-Cope-Prod. Both the *syn*- and *anti*-TS2 arrange to form a chair-like structure, with the fluorine atom preferentially being in the axial (F-*Syn*-TS2) position due to favorable hyperconjugation from the C_1-H s-bond.

But, on the other hand, formation of the 3-Exo-Tet-Prod **96** is highly endergonic due to the large enthalpy of formation of fluoride. The formation of the enamide is prevented due to the unfavorable *E*-arrangement of the C_4 ester and C_5 methyl groups along the newly formed C_4-C_5 π-bond (Scheme 14). To form the enamide intermediate **100**, this region of the substrate must rotate inward toward the imine bond, which would place the methyl group inside the forming cyclohexane ring. However, for the N_3/SMe/SCF_3 substrates, these groups are in a *Z*-arrangement, which rotates the methyl group out of the forming ring **101**. If these groups were in a *Z*-arrangement, the formation of the enamide product would be facile.

The rearrangement mechanism for the chloro-substrate Cl-React follows a similar path to that of the fluoro-substrate in that the *syn*-Cope product **92** is observed, however following the formation of the Cope-product the substrate reorganizes to form the 3-Exo-Tet-Prod. The *syn*- and *anti*-TS2 arrange to form chair-like structures, with the chlorine atom preferentially being in the axial (Scheme 13) position due to favorable hyperconjugation from the C_1-H s-bond. The Cl-*syn*-Cope-Prod is prevented to form the enamide intermediate due to the same steric restrictions of the C_4 ester and C_5 methyl groups, similar to that of the fluoro-substrate. However, the barrier to form the 3-*exo-tet* is nearly isoenergetic to Cl-*syn*-TS2, and the formation of a chloride is much more thermodynamically favorable to that of the Cl-Enamide-Pro and methoxy anion (Table 5).

In summary, calculated structures, supported by experimental results, lead us to the following conclusions: (1) The stepwise dissociation–recombination mechanism was found to be favored. The stereochemistry of the chiral auxiliary

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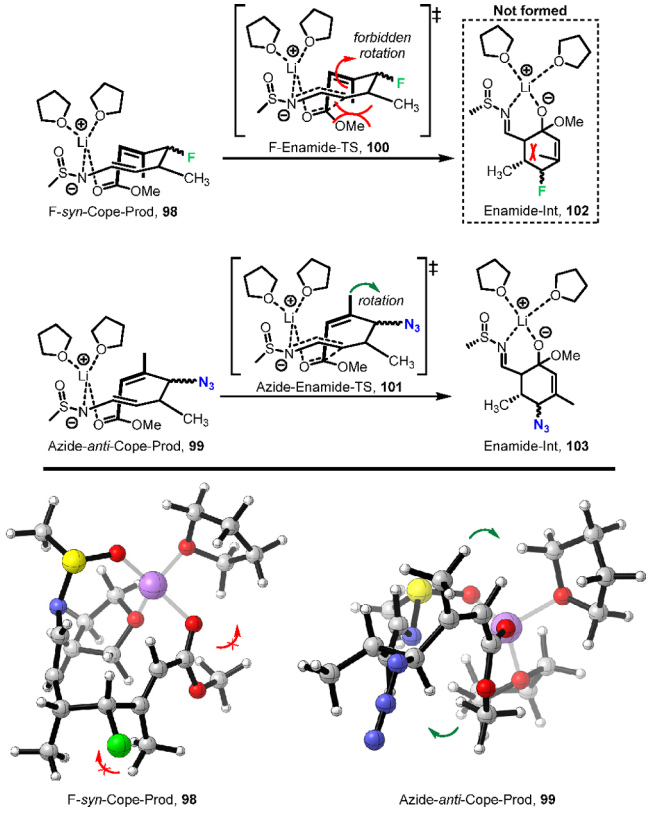
Scheme 14. γ-N_3-Substituent Promotes Enamide Cyclization

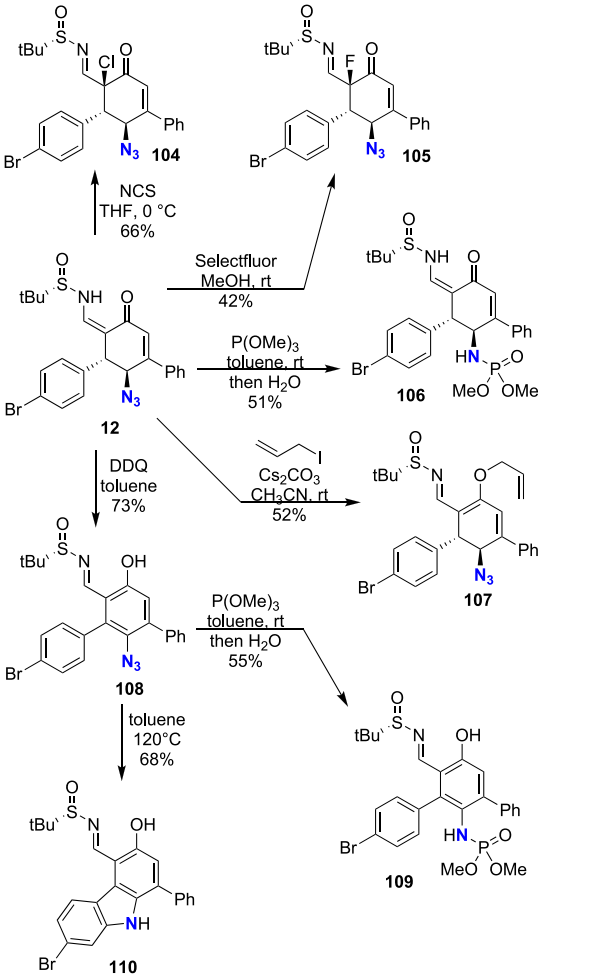


determines the stereochemistry of the Cope product by influencing the orientation of the lithium dienolate and sulfinylimine fragments in the recombination step. (2) For the N_3/SMe/SCF_3 substrates, the *anti*-Cope product formation is preferred over *syn* with an azide group in the equatorial position to avoid steric clashes with the methyl group. Because of this equatorial placement of the azide group, a favorable *Z*-arrangement between the C_4 ester and C_5 methyl groups can be achieved, which further cascade to form the enamide species. (3) In the case of halogens (X= F, Cl, and Br), the *syn*-Cope product formation is preferred over *anti* with the halogen group in the axial position due to favorable hyperconjugation from the C_1−H s-bond. This axial preference of the halogen groups further prevents the enamide formation because it requires an unfavorable inward rotation around the C_5 methyl group toward the imine bond.

APPLICATION EXAMPLES

Highlighted in Scheme 15 are interesting reaction transformation examples for azide-substituted cyclohexenone amino-Cope product **12**. Treatment of **12** with electrophilic halogen reagents such as *N*-chlorosuccinimide (NCS) and selectfluor affords chloro- and fluoro-substituted products **104** and **105**, respectively, as single diastereomers. The Staudinger reaction is realized with trimethyl phosphite,[30] which following in situ hydrolysis yields amino-phosphate **106**. Selective O-allylation can be achieved using allyl iodide and cesium carbonate as base (**107**). Dehydrogenation to form aryl azide **108** takes place in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Aryl azide **108** readily undergoes a Staudinger reaction to yield aminophosphate **109**. Alternatively, heating of **108** in toluene forms a nitrene, which inserts into a C−H bond of the neighboring bromo-aryl group to deliver carbazole **110**.[31]

Scheme 15. Examples of Transformations for a Representative Azide-Substituted Amino-Cope Product



CONCLUSIONS

In summary, we have further established and expanded upon the great synthetic promise of our new lithium-enabled asymmetric amino-Cope rearrangement cascade. By exploring dienolates substituted with a range of γ-substituents, we have uncovered most intriguing selectivity outcomes, wherein γ-azide, thiomethyl, and trifluoromethylthio substituents proceed via a chair amino-Cope transition state to form chiral cyclohexenone products with two new stereocenters with an *anti*-relationship. Intriguingly and unexpectedly, the corresponding γ-halo (F, Cl, and Br) dienolate substituents also undergo the proposed lithium-enabled asymmetric amino-Cope cascade but form products with a *syn*-relationship between the two new stereocenters as well as an E-enoate. In the case of chlorides and bromides, the intermediate lithium enamide undergoes a remarkably facile 3-*exo-tet* cyclization to form cyclopropane products. Further explorations on the extremes of the size and electronics of γ-substituents revealed that electron donating groups such as methyl, methoxy, and trifluoroethoxy proceed to only undergo the initial Mannich step or undergo unselective conjugate additions. Interestingly and of great interest is the diverted pathway a nitro-substituted

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enoate undergoes to yield valuable β-lactam products. It is evident that exciting adventures and discoveries await to be unraveled for this new asymmetric amino-Cope reaction platform.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00745.

Experimental procedures, characterization data, and spectroscopic data for all new compounds and computational methods (PDF)

Accession Codes

CCDC 2017739−2017740 and 2039911−2039912 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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