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# Stereoselective Synthesis of Conjugated Di- and Trienamides via a Dienolate Enabled Anionic Cascade

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Cite This: J. Org. Chem. 2023, 88, 17485−17488 Read Online

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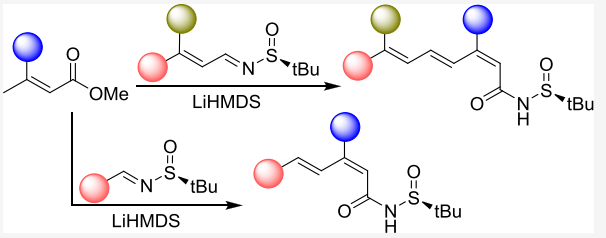
**ABSTRACT:** We report a stereoselective synthesis of conjugated di- and trienamides from the direct one pot γ-selective union of a dienolate and chiral nonconjugated and conjugated sulfinyl imines, respectively. This class of anionic cascades was uncovered as part of efforts to challenge the steric limitations of an anionic asymmetric amino-Cope rearrangement platform. Reaction scope studies have uncovered the substitution patterns essential for starting chiral tri- and *Z*-disubstituted conjugated and nonconjugated sulfinyl imines to be matched for the anionic cascade. Mechanistic studies indicate that, following an initial γ-dienolate Mannich attack, an intermediate 5,6-dihydropyridin-2(1*H*)-one is formed and then ring-opened.

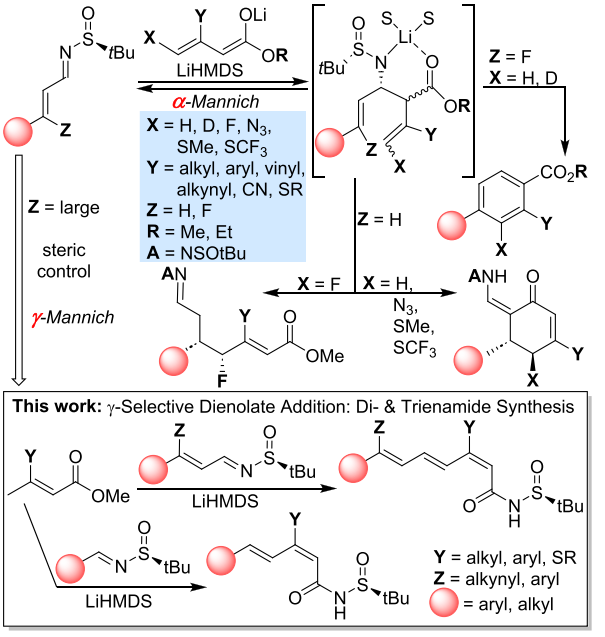





## INTRODUCTION

In 2017, our group revived the forgotten area of anion-accelerated amino-Cope rearrangement chemistry[1−5] with the demonstration that high-yielding selective asymmetric outcomes could be realized by using a counterion (lithium) to ensure a reliable merger of chiral sulfinyl imine[6] and dienolate reaction partners.[7] This anionic reaction cascade proceeds via an initial reversible α-Mannich addition, wherein only the matched lithium counterion guided adducts proceed to undergo the amino-Cope rearrangement chemistry to afford diastereomerically pure cyclic and acyclic products (Scheme 1). We have since demonstrated that the sulfinyl imine starting-material synthesis can be significantly streamlined[8] and that a second stereocenter (X = F, $N_3$, SMe, and $SCF_3$)[9] can be incorporated into this anionic asymmetric amino-Cope cascade with the resulting products readily converted into highly substituted aromatic products.[10] Recently, we have focused our efforts on pushing the steric and electronic limitations of the amino-Cope cascade by investigating trisubstituted sulfinyl imines (Z ≠ H), which has revealed that β-fluoro imines (Z = F) do indeed proceed through the amino-Cope cascade to form benzoate ester products.[11] These investigations revealed that, for larger alkyl groups (Z = alkyl), the α-Mannich addition proceeded but no amino-Cope rearrangement then ensued, only retro-Mannich. In this study, we report that, if smaller "alkyl" groups in the form of alkynes (Z = alkynes) are employed, the dienolate now proceeds to undergo a selective γ-Mannich addition to the sulfinyl imines to afford trienamide products as single stereoisomers. In this study, we have further used these insights to establish that sterically congested Z- and nonconjugated sulfinyl mines are also matched reaction

**Scheme 1. Dienolate-Enabled Asymmetric Anionic Amino-Cope Cascades: Stereoselective Dienolate γ-Mannich Addition Route to Di- and Trienamides**




Received: October 12, 2023
Revised: November 14, 2023
Accepted: November 22, 2023
Published: December 4, 2023





https://doi.org/10.1021/acs.joc.3c02327
J. Org. Chem. 2023, 88, 17485−17488

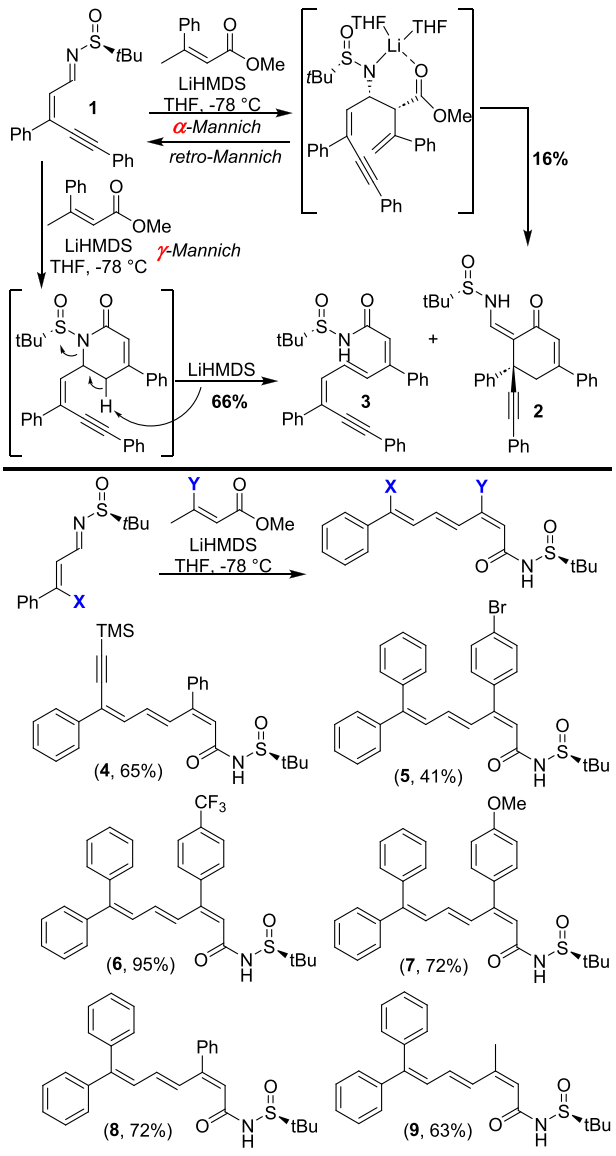
partners for this class of di- and trienamide-forming anionic cascades.

## RESULTS AND DISCUSSION

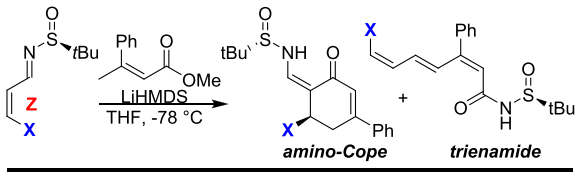
In earlier attempts to form all-carbon quaternary centers using our anionic amino-Cope cascade, we had observed for trisubstituted imines containing $\beta$-alkyl groups that they readily underwent an $\alpha$-Mannich addition but then did not proceed to amino-Cope products but instead only retro-Mannich pathways. Before giving up on this important synthetic goal, we decided to evaluate trisubstituted imines containing "smaller" carbon substituents, namely, Csp-hybridized ones, as they are smaller than their corresponding $Csp^2$ and $Csp^3$ substituents. Requisite conjugated sulfinyl imines (**1**, Scheme 2) were made by subjecting acetophenone to Vilsmeier–Haack ($PBr_3$, DMF) followed by imine formation and Sonogashira coupling with the resulting $\beta$-bromo imine (see the Supporting Information). Treatment of imine **1** with our standard amino-Cope reaction conditions remarkably for the first time delivered an all-carbon quaternary center containing amino-Cope product (**2**), albeit in a low 16% isolated yield. More importantly, an unexpected new product, which was shown to be trienamide **3** was isolated in a 66% isolated yield as a single isomer. In this anionic cascade, the extra alkyne substitution proved to be sufficient to divert the dieanolate nucleophile from its regular $\alpha$-Mannich addition pathway to a selective $\gamma$-Mannich addition/cyclization, resulting in the formation of an intermediate 5,6-dihydropyridin-2(1*H*)-one, which then presumably underwent a second deprotonation of a $\gamma$-proton of the N-heterocycle to break the C–N bond and form trienamide **3** with the last double bond selectively formed as E. Equipped with these structural insights, we were able to find rare overlooked examples of the aldehyde variant in the literature.[12,13] With complete confirmation of the structure of trienamide **3** and with a firm mechanistic postulate to guide reaction optimizations, it was clear that a minimum of 2 equiv of base (LiHMDS) would be required for this anionic cascade. Optimizations quickly revealed that using 3 equiv of LiHMDS and 1.5 equiv of a $\beta$-substituted conjugated butanoate nucleophile delivered reliable consistent results. This result was confirmed as well for TMS-alkyne (**4**) and for larger diphenyl imines as well (**5**–**9**), wherein the importance of the enoate aryl group electronics had a significant impact on the overall yield.

In our 2017 inaugural amino-Cope publication,[7] we demonstrated that a phenyl-substituted Z-sulfinyl imine (**8**) was compatible with the amino-Cope anionic cascade (60%; Scheme 3). We wondered if, by increasing the size of the Z-imine substituent, a turning point could be identified wherein the amino-Cope pathway would be suppressed in favor of the trienamide $\gamma$-Mannich addition pathway. Imine substrates used in this study were made from corresponding aldehydes via a Corey-Fuchs alkyne synthesis[14] involving in situ trapping with DMF followed by immediate sulfinyl imine formation and Lindlar catalyst alkyne reduction (see the Supporting Information). Gratifyingly, we uncovered a most intriguing steric trend wherein approximately equal amounts of amino-Cope (**17**) to trienamide (**19**) products are observed for Z-isopropyl-substituted sulfinyl imines (**12**). The ratio of products tilted slightly toward trienamide (**20**) with the

**Scheme 2. Discovery of the Trienamide-Forming Anionic Cascade via $\gamma$-Mannich Addition**




**Scheme 3. Impact of the Substituent Size of Z-Sulfinyl Imines on the Ratio of Amino-Cope versus Trienamide Products**




| X = | amino-Cope | trienamide |
|---|---|---|
| (**10**) | (**15**, 60%) | Not observed |
| (**11**) | (**16**, 42%) | Not observed |
| (**12**) | (**17**, 27%) | (**19**, 35%) |
| (**13**) | (**18**, 15%) | (**20**, 40%) |
| (**14**) | Not observed | (**21**, 65%) |



https://doi.org/10.1021/acs.joc.3c02327
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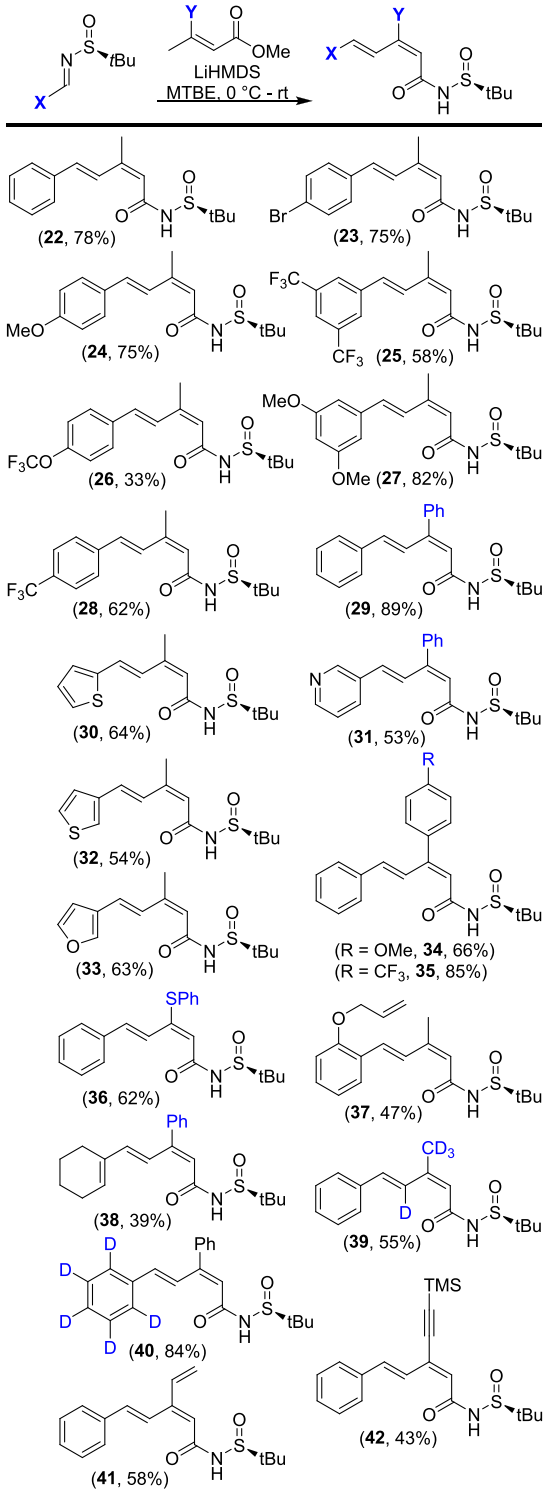
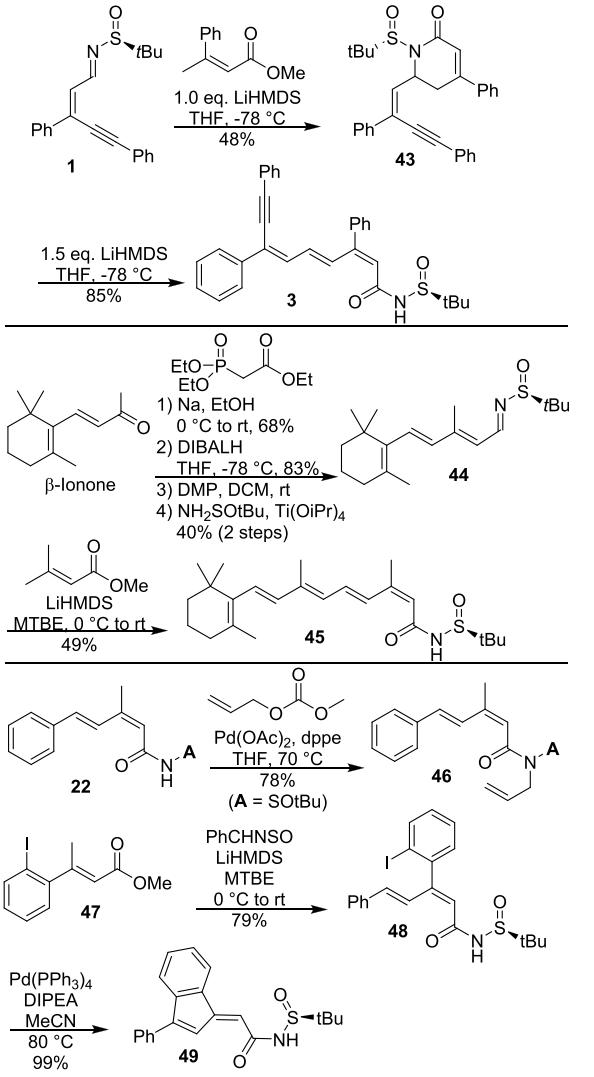
**Scheme 4. Anionic Cascade Substrate for Scope Non-conjugated Imines**




cyclohexyl-substituted imine (**13**) used, and then an exclusive formation of trienamide (**21**) with a *t*-butyl-substituted sulfinyl imine (**14**) occurred.

With the trienamide forming reaction platform established, we wondered if this anionic cascade could also be applied to nonconjugated imines. We were delighted to learn that, when we subjected phenyl sulfinyl imine to our standard reaction conditions using methyl 3,3-dimethyl acrylate as the dienolate

**Scheme 5. Mechanistic Insights and Anionic Cascade Applications**




source, a dienamide product **22** was formed in a 78% isolated yield (Scheme 4). As evident from the 20 dienamide products presented in Scheme 4, a variety of aryl, heteroaryl, and cyclohexenyl imines are compatible with this procedure as are different butenoate substituents such as methyl, phenyl, aryl (**34** and **35**), thiophenyl (**36**), alkenyl (**41**), and alkynyl (**42**). This robust reaction also lends itself well for design incorporation of deuterated substituents (**39** and **40**), which are of great interest and growing importance in the pharmaceutical industry.[15,16]

To gain further insights into the steps involved in the trienamide anionic cascade, we subjected alkyne-containing sulfinyl imine **1** to our cascade conditions with only 1.0 equiv of base (LiHMDS) instead of 3 equiv, which allowed us to confirm the presence of the proposed 5,6-dihydropyridin-2(1*H*)-one cascade intermediate **43**, obtaining a 1:1 mixture of diastereomers (Scheme 5). Subjecting **43** to 1.5 equiv LiHMDS led to a facile ring-opening and clean formation of trienamide **3** in an 85% isolated yield. Retinamides (amide forms of retinoic acid) have shown promise in cancer treatment,[17] and as part of these studies, the role of the olefin geometry of the terminal olefin (13-*cis* vs 13-*trans*) has been studied. Presented in Scheme 5 is a 13-*cis* retinamide target


https://doi.org/10.1021/acs.joc.3c02327
J. Org. Chem. 2023, 88, 17485−17488

application of our stereoselective dienamide-forming reaction, which is realized by converting imine (**44**) that is obtained from $\beta$-ionone directly to **45**. Selective palladium-catalyzed N-allylation[18] of the dienamide framework can be realized with allyl carbonate to afford **46** in a high yield. This reaction lends itself well to future design applications with a specific incorporation of functional groups such as orthoaryl substituents on either the imine or enoate nucleophiles. Toward that end, 3-aryl butanoate **47** was shown to react efficiently with the Ellman imine of benzaldehyde to afford dienamide product **48**, which proceeds to undergo a near-quantitative Heck cyclization to afford **49** as a single isomer.

## CONCLUSIONS

In conclusion, we report a stereoselective anionic cascade for assembling di- and trienamide products by the base-mediated union of specific classes of sulfinyl imines and dienolates. Although this reaction works perfectly well with racemic imines, we chose to highlight this reaction with chiral sulfinyl imines as further synthetic application opportunities might arise for them in the resulting products. Given the ready availability, cost, and stability of sulfinyl imines, the enoate nucleophiles, and the use of a simple lithium base, this reaction represents a powerful entry into an efficient assembly of conjugated organic architectures.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c02327.

Detailed experimental procedures, characterization, and spectroscopic data for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We would like to thank the National Science Foundation (no. CHE-2153657) for supporting this research project and for the purchase of a NMR spectrometer (MRI grant no. CHE-1920234).

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