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Asymmetric Vinylogous Aza-Darzens Approach to Vinyl Aziridines

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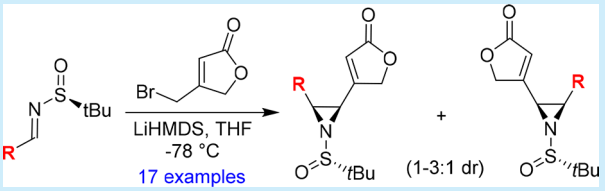
Supporting Information

ABSTRACT: A new asymmetric approach to assemble *cis*-vinyl aziridines is reported. A reaction of strategically substituted dienolates, decorated with a γ-leaving group, with chiral sulfinimines afforded chiral vinyl aziridine products in good to excellent yields. This is the first systematic study toward the realization of a useful asymmetric vinylogous aza-Darzens reaction. The reaction is initiated by a *syn*-selective addition, affording *cis*-vinyl aziridine products after displacement of bromide. The low *syn*-diastereoselectivity is attributed to competing retro-Mannich pathways.

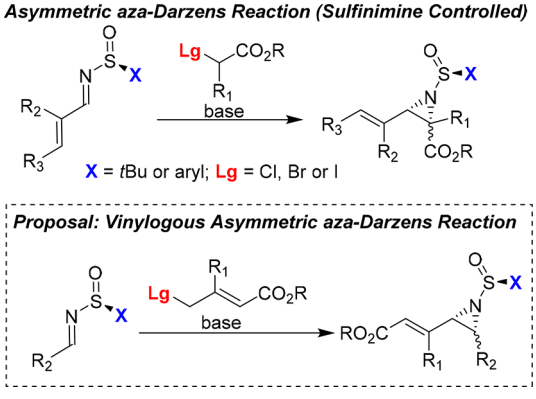


Our group's interest in developing new metal-catalyzed ring openings of strained rings[1] has over the years motivated us to carefully assess the state-of-the-art of synthesis for how to best assemble the requisite strained ring starting materials. In the context of synthesizing chiral vinyl aziridine precursors efficiently and selectively for our studies, this challenge has been particularly interesting to ponder as many obstacles remain unsolved or not ready for practical applications. For our first vinyl aziridine ring expansion studies employing chiral substrates, we concluded that the most well-suited chiral aziridine synthesis approaches available at the time were the aza-Darzens[2] chiral sulfinamide approach developed by Davis[3] and the Corey−Chaykovsky-type method designed by Aggarwal.[4] Inspired by the work of Stockman,[5] we employed Ellman's *t*-butyl sulfinamide auxiliary[6] for our aza-Darzens studies (Scheme 1, top).[7] By coupling this aziridine approach with our ring expansion reaction, we were able to assemble chiral 3-pyrroline structures.

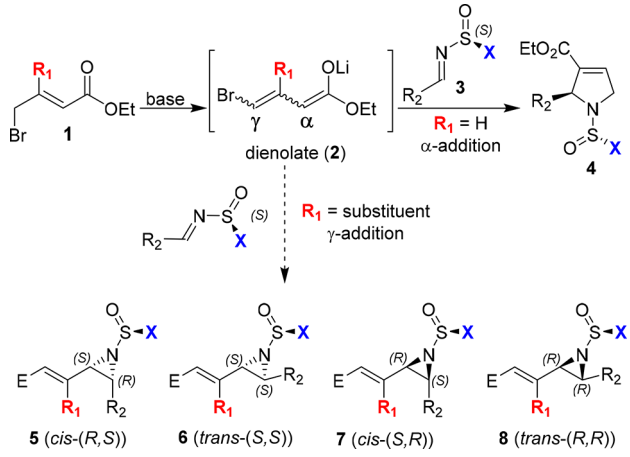
As our needs for more diverse and complex chiral vinyl aziridines grew, the limitations of our first approach motivated us to consider ways to expand it, which brought us to a surprising void in the literature, namely, the vinylogous asymmetric aza-Darzens reaction (Scheme 1, box).[8] In this approach, the double bond destined for the vinyl aziridine is moved from the electrophile (chiral sulfinimide) to the nucleophile (acrylate), and the halide leaving group is in the γ-position instead of the α-position. For this proposal to be successful, the resulting dienolate needs to attack the chiral imine electrophile from its γ-position. The resulting vinyl aziridine products would provide new substituent patterns that are not possible with the earlier approaches.

Scheme 2 outlines our synthetic design along with the regio- and stereochemical obstacles we needed to overcome. We learned in an earlier study that when the dienolate of 4-bromoacrylates was not substituted (R_1 = H), an α-initiated addition cascade ensued to form chiral pyrroline products.[9] We proposed that by adding a substituent in the β-position we could divert the dienolate addition to the more stable γ-addition

Scheme 1. Vinylogous Asymmetric Aza-Darzens Proposal



Scheme 2. Mechanistic Challenges: Choice of Nucleophile



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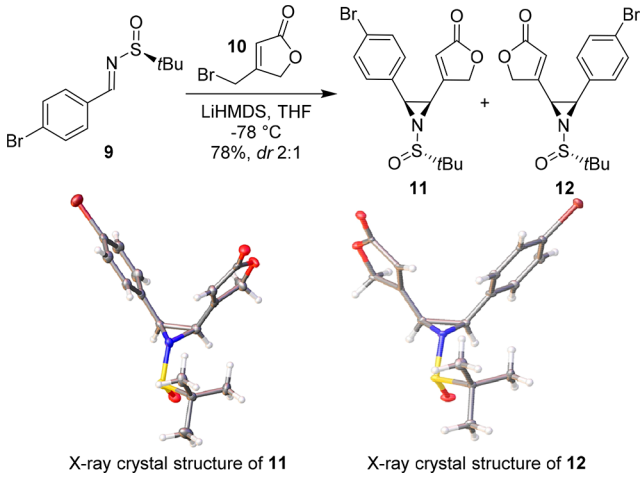
products, setting the stage for in situ cyclization to complete the asymmetric aza-Darzens cascade. In our design, the role of the chiral sulfinamide auxiliary is to enable selective dienolate imine addition, hopefully favoring a single product out of eight possibilities (four shown containing *E* double bond).

We chose bromo-substituted butenolide **10** as the dienolate precursor (Scheme 3). We postulated that its cyclic structure

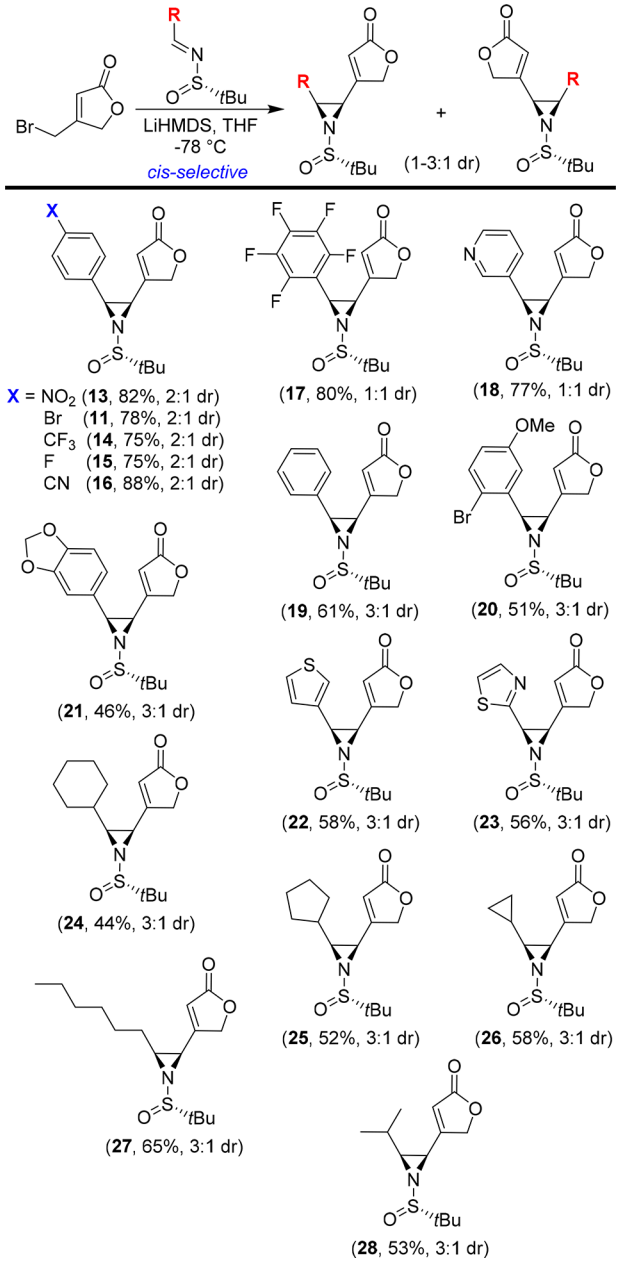
Scheme 3. Vinylogous Asymmetric Aza-Darzens Reaction



would favor conjugation with the lactone and therefore γ-attack of its dienolate. We were delighted to learn that our asymmetric vinylogous aza-Darzens hypothesis could indeed be realized upon treatment of **10** with lithium bis(trimethylsilyl)amide (LiHMDS) in the presence of chiral sulfinamide **9**. It is critical to add base slowly to a mixture of the imines and the butenolide to suppress self-dimerization of the nucleophile. Two vinyl aziridine products (**11** and **12**) were formed in a 2:1 ratio and very good isolated overall yield (78%). Gratifyingly, the structures as well as the absolute and relative stereochemistry of these two products could be unambiguously determined following single-crystal X-ray analysis. This analysis revealed that the addition of the dienolate, resulting from deprotonation of butenolide **10**, to chiral sulfinamide **9** is *syn*-selective,[10] affording after cyclization *cis*-aziridine products **11** and **12**. This addition outcome was a bit surprising as in our earlier aza-Darzens studies[7] using similar chiral imines and the enolate of *t*-butyl α-bromoacetate as the nucleophile, a mixture of *cis*- and *trans*-vinyl aziridine products resulted, both of which had originated from attack of the nucleophile from the same imine face.

We next set out to determine the scope of this new asymmetric vinylogous aza-Darzens reaction. Seventeen examples, wherein aromatic and alkyl imines varying in size and electronics, are presented in Scheme 4. In all cases, only the *cis*-vinyl aziridine products are isolated (major isomer shown). A series of interesting observations can be deduced from the reactivity and selectivity trends. For example, aromatic imines on average afford *cis*-aziridine products (**11**–**23**) in yields higher than those of their alkyl imine (**24**–**28**) counterparts. Within the aromatic series, electron-deficient aromatic imines perform the best, with electron-rich aromatic imines being lower yielding. With respect to diastereoselectivity, the story is reversed, with alkyl imines affording *cis*-aziridine products uniformly in a 3:1 ratio, whereas most aromatic imines yield *cis*-aziridine products in a 1:1 to 3:1 ratio, with electron-rich imines mirroring the selectivity of alkyl imines.

Scheme 4. Vinylogous Asymmetric Aza-Darzens Reaction Scope[a]



[a]Reaction conditions: LiHMDS (2.0 equiv) added slowly at −78 °C to a mixture of **10** (1.5 equiv) and chiral imine (1.0 equiv). Isolated yields, with major diastereomer shown.

Apart from the low cost of the chiral sulfinamide auxiliary,[11] the most attractive application feature of this asymmetric vinylogous aza-Darzens vinyl aziridine approach is that it is not limited to chiral pool sources, affording access to either vinyl aziridine enantiomeric series. Shown in Scheme 5 are two examples (**29** and **30**), wherein the enantiomeric imine is employed. The same trend is observed with these alkyl imines, with the vinyl aziridine products isolated in good yields and 3:1 diastereoselectivity.

Inspired by the success of the dienolate originating from butenolide **10**, we set out to explore an acyclic variant (**31**, Scheme 6). For 3,3-dimethyl acrylate derivative **31**, it was quickly realized that self-dimerization was a much larger

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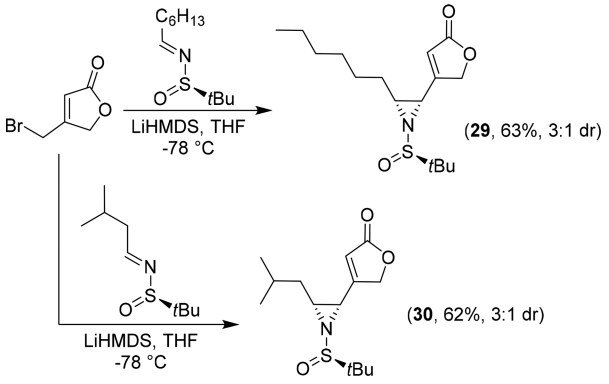
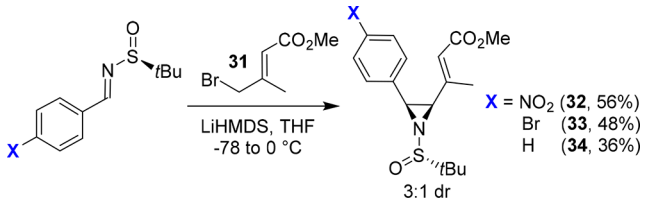
Scheme 5. Auxiliary Enables Access to Enantiomeric Series



Scheme 6. Altering Nucleophile Impacts Reaction Yields



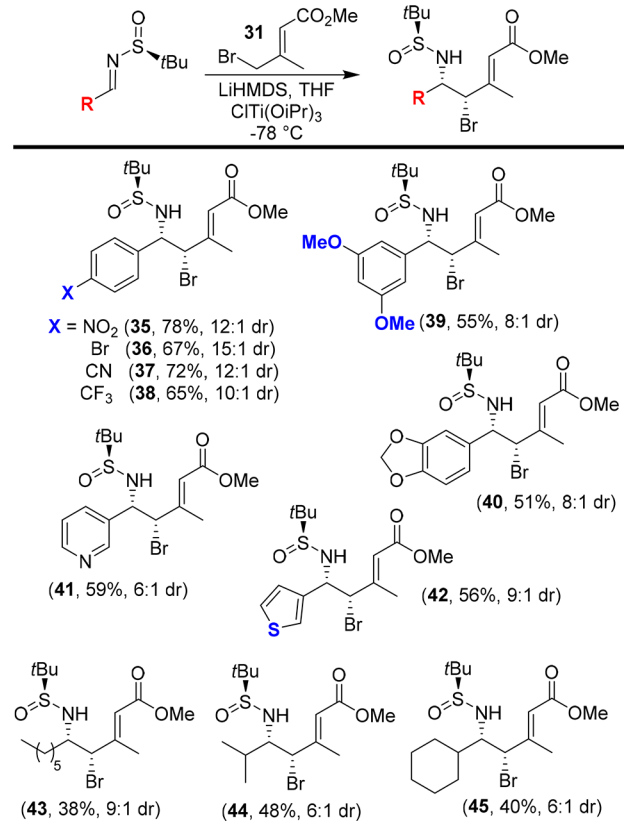
challenge than with its butenolide counterpart. This self-condensation is partly responsible for the fact that, although the products of this nucleophile were similarly *cis*-vinyl aziridines, yields were significantly lower. Diastereoselectivity for these three products was slightly higher.

We next set out to explore if this asymmetric vinylogous aza-Darzens cascade could be accomplished with higher diastereoselectivity by following a stepwise approach, which in turn we hoped would help us understand why the two *cis*-vinyl aziridine products are preferentially formed. We postulated that Ellman's titanium enolate approach[12] to asymmetrically assemble β-amino acids might enable us to separate the Mannich addition step from the aziridine cyclization step. We were pleased to learn that not only was this titanium enolate approach γ-selective (Scheme 7) but it also delivered the addition products in much higher diastereoselectivity (6:1 to 15:1) than what we had observed for the vinylogous aza-Darzens cascade (1:1 to 3:1). Electron-deficient aromatic imines afforded vinyl aziridine products (**35**–**38**) in the highest yield and diastereoselectivity. NMR coupling constant analysis and cyclization explorations confirmed that the titanium enolate addition was *syn*-selective.

With γ-selective addition products with high diastereoselectivity delivered via the titanium enolate addition, we were able to separately explore the aziridine cyclization step (Scheme 8). Treatment of diastereomerically enriched Mannich product **35** (12:1 dr) with our standard base (LiHMDS), under the same reaction conditions as our aza-Darzens cascade, afforded vinyl aziridine **32** in only 32% isolated yield and 3:1 diastereoselectivity. The low yield and loss of diastereoselectivity serves as confirmation of a competing retro-Mannich reaction pathway. Further support of this hypothesis was the fact that the imine isolated from this reaction was no longer a single *E*-isomer, but a mixture of *E*- and *Z*-isomers. Other bases performed even worse, affording less vinyl aziridine and imine mixtures.[13]

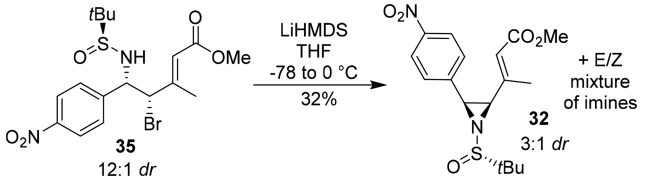
We have also carefully investigated the behavior of **35** in the presence of LiHMDS as a function of temperature. No cyclization takes place at −78 °C, and when −50 °C is reached, a complete retro-Mannich reaction takes place. Further warming

Scheme 7. Titanium Enolate-Mediated Mannich Reactions[a]



[a]Reaction conditions: Chiral imine (1.0 equiv) added to a −78 °C solution of ester (2.0 equiv), LiHMDS (2.5 equiv), and $ClTi(OiPr)_3$ (5.0 equiv). Isolated yields, with major diastereomer shown.

Scheme 8. Vinyl Aziridine Cyclization Studies



of this mixture results in less selective enolate addition and cyclization to vinyl aziridine **32**.

Taken together, our data strongly suggest that retro-Mannich steps resulting in the formation of chiral imine mixtures are the main reason for lower than expected diastereoselectivity (Scheme 9). The dienolate can add to the chiral imine from either its kinetic α- or thermodynamic γ-positions. With no α-addition or 3-pyrroline products isolated, we can postulate that any α-addition intermediates generated all underwent a retro-Mannich reaction to re-form the imine and the dienolate.[14] With the γ-addition pathway eventually preferred, the resulting addition products now have a choice between irreversible cyclization to the vinyl aziridine products or alternatively to re-form the imine and the dienolate via a retro-Mannich step. Our cyclization studies originating with the pure diastereomer isolated from the titanium addition step support the hypothesis that the retro-Mannich pathway is responsible for lower yields and diastereoselectivity. This type of retro-Mannich reaction for chiral sulfonamides has been observed by Davis[15] and, most

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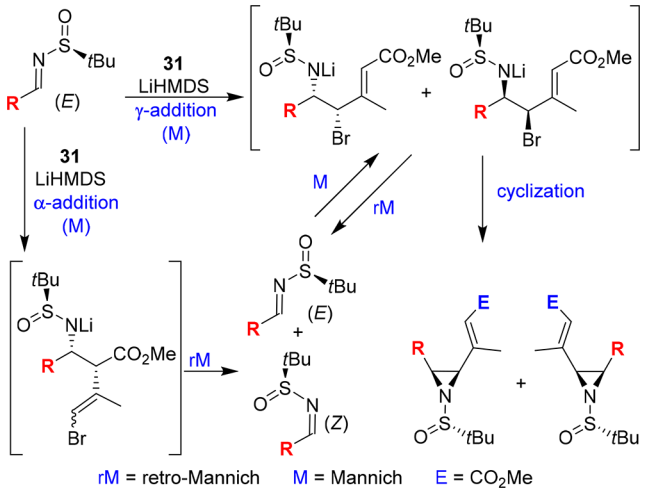
Scheme 9. Mechanistic Proposal



recently, in our asymmetric amino-Cope rearrangement studies.[13]

In summary, we report an asymmetric vinylogous aza-Darzens approach for constructing vinyl aziridines. This robust reaction is enabled by a chiral sulfinamide auxiliary and a strategic β-substitution of a 4-bromo-substituted dienolate nucleophile. Yields are good to very good when a butenolide nucleophile is employed. This new reaction affords *cis*-vinyl aziridines, with diastereoselectivity dependent on the electronics and sterics of the starting imine as well as isomerization of the imines via competing retro-Mannich pathways.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02074.

Experimental procedures (PDF)

Accession Codes

CCDC 1451253 and 1451353 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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I.C. and P.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(13) Interestingly, the titanium enolate of **10** affords aziridine **13** directly upon warming to −65 °C in a low but reversed 1:2.7 ratio.

(14) Our amino-Cope studies, which utilize the same nucleophile (**31**), confirm that α-addition to the chiral sulfinamide takes place first. In the present situation, the intermediate does not have a Cope pathway available, which is why a retro-Mannich reaction occurs instead. Chogii, I.; Das, P.; Fell, J. S.; Scott, K. A.; Crawford, M. N.; Houk, K. N.; Njardarson, J. T. *J. Am. Chem. Soc.* **2017**, *139*, 13141−13146.

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