JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

New Class of Anion-Accelerated Amino-Cope Rearrangements as Gateway to Diverse Chiral Structures

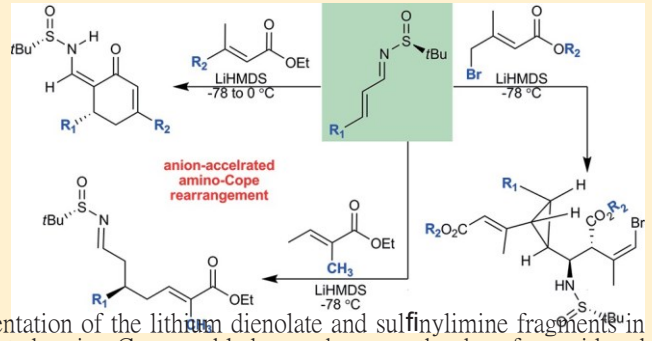
Isaac Chogii,[‡] Pradipta Das,[‡] Jason S. Fell,[†] Kevin A. Scott,[§] Mark N. Crawford,[‡] K. N. Houk,*[,†] and Jon T. Njardarson*[,‡]

[‡]Department of Chemistry and Biochemistry and [§]Department of Pharmacology and Toxicology, University of Arizona, Tucson, Arizona 85721, United States

[†]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

Supporting Information

ABSTRACT: We report useful new lithium-assisted asymmetric anion-accelerated amino-Cope rearrangement cascades. A strategic nitrogen atom chiral auxiliary serves three critical roles, by (1) enabling in situ assembly of the chiral 3-amino-1,5-diene precursor, (2) facilitating the rearrangement via a lithium enolate chelate, and (3) imparting its influence on consecutive inter- or intramolecular C−C or C−X bond-forming events via resulting chiral enamide intermediates or imine products. The mechanism of the amino-Cope rearrangement was explored with density functional theory. A stepwise dissociation−recombination mechanism was found to be favored. The stereochemistry of the chiral auxiliary determines the stereochemistry of the Cope product by influencing the orientation of the lithium dienolate and sulfinylimine fragments in the recombination step. These robust asymmetric anion-accelerated amino-Cope enabled cascades open the door for rapid and predictable assembly of complex chiral acyclic and cyclic nitrogen-containing motifs in one pot.



INTRODUCTION

The oxy-Cope rearrangement[1] is an important transformation in organic chemistry whose applications and impact grew rapidly following the disclosure of an anion-accelerated variant by the David Evans group[2] in 1975.[3] The corresponding 3-amino-Cope rearrangement has not received much attention in the last 40 years[4] despite the obvious opportunities for designing asymmetric variants and the attractive bond-forming potential of the resulting enamine products (Figure 1).

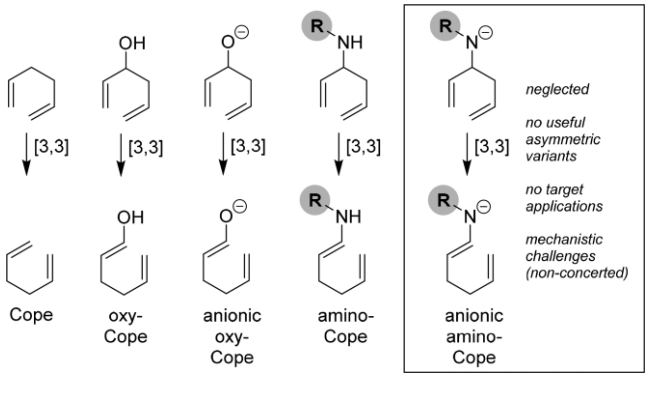


Figure 1. Anion-accelerated amino-Cope rearrangement: a neglected class of sigmatropic rearrangements.

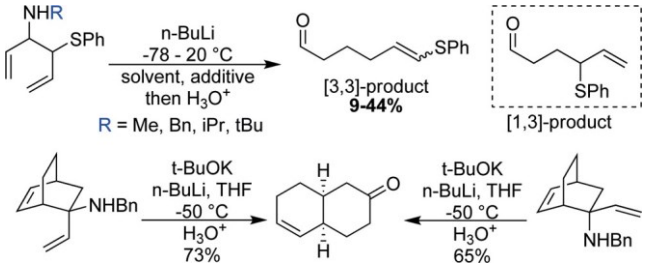
Three research groups have briefly investigated the anion-accelerated amino-Cope reaction, but as of yet these contributions have not captured the attention of the broader synthetic chemistry community. Insights from these early contributions help paint a picture of why adaptation of Evans' observations in regard to the 3-amino variant is not as straightforward as one might gather. The first report from a team of Merck−Frosst scientists demonstrated, for a specific series of *N*-alkyl-substituted substrates,[5] the feasibility of this reaction and that it proceeded at far lower temperatures than the anionic-oxy Cope rearrangement. These low-yielding reactions (9−44%) were mainly plagued by a competing [1,3]-rearrangement, which strongly suggested a nonconcerted pathway (Scheme 1). Inspired by this study, Meyers and Houk evaluated the anionic rearrangement behavior of several 3-amino-Cope substrates.[6] These substrates failed to rearrange; instead, they either did not react, decomposed, or deallylated. A rigorous computational investigation concluded that the anionic 3-amino-Cope rearrangement proceeds via a stepwise mechanism wherein the 3-amino-1,5-diene dissociates and then recombines.

Allin reported that a chiral auxiliary could be used for the anion-accelerated amino-Cope rearrangement (Scheme 2).[7] Unfortunately, elevated temperatures were required and

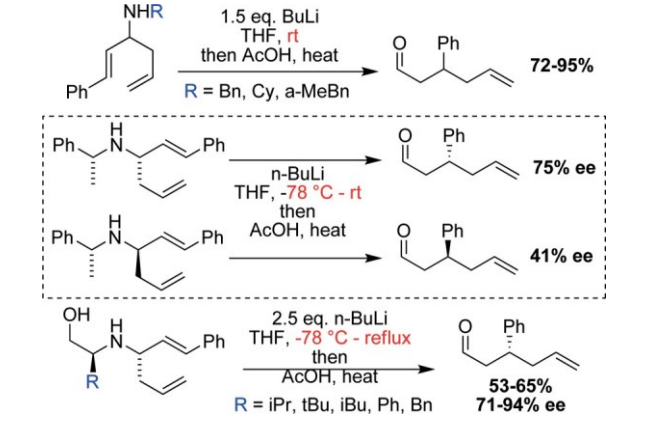
Received: July 13, 2017
Published: September 8, 2017

DOI: 10.1021/jacs.7b07319

Scheme 1. First Anion-Accelerated Amino-Cope Rearrangements Example (Merck−Frosst, 1993)[5]



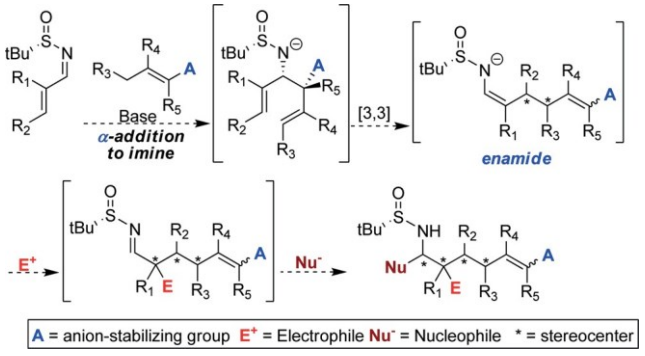
Scheme 2. Only Reported Asymmetric Anion-Accelerated Amino-Cope Rearrangement Studies (Professor Allin)[7]



significant stereochemical erosion was observed when chiral *N*-benzyl substituents were employed. Optimizations revealed that amino-alcohol chiral auxiliaries could somewhat improve this erosion challenge, but this was accomplished at a cost of using excess *n*-butyl lithium and much higher (reflux) temperatures. Reaction outcomes varied greatly when substrate substituents were altered.[8] Allin also concluded that the rearrangement proceeded through a nonconcerted pathway. Neither the Merck−Frosst group nor Allin attempted to harness the reactivity of the resulting enamide intermediate or imine product.

It is evident that the anion-accelerated amino-Cope rearrangement can be realized, but multiple significant obstacles need to be addressed for it to be a useful synthetic tool. Perhaps the most challenging of these obstacles is highlighted by experimental and computational data that strongly suggest a nonconcerted mechanism, wherein the amino-diene undergoes a heterolytic cleavage followed by reunification in one of two ways (net [3,3]- or [1,3]-rearrangement) or fully dissociating. Arguably, the most impactful substituent for this reaction is the nitrogen atom substituent. To date, only a handful of alkyl substituents have been evaluated, none of which have proven to be a good match. We propose that judicious choice of the appropriate chiral *N*-substituent could not only address the aforementioned rearrangement challenges but also enable assembly of the chiral 1,5-amino-diene Cope precursor in situ. Inspired by the success of our recent one-pot asymmetric synthesis of 3-pyrrolines,[9] we postulated that a chiral sulfinamide[10] group might represent a suitable nitrogen atom substituent. The auxiliaries used to form such imines are stable, inexpensive,[11] and readily available in both enantiomeric forms. We envisioned that anion-stabilized nucleophiles could selectively add to the chiral imine and that the resulting α-adduct would then undergo an anion-accelerated 3-amino-Cope rearrangement (Scheme 3). The resulting chiral enamide could then be trapped in the same pot by an electrophile in an inter- or intramolecular fashion. The chiral auxiliary could at this point be used to control a fourth consecutive step by treatment of the chiral imine with a nucleophile. In this proposed anionic cascade, the chiral auxiliary strategically directs all four steps (α-addition, rearrangement, enamide trapping, and imine addition) enabling access to a diverse array of complex chiral cyclic and acyclic products with multiple useful functional group handles.

Scheme 3. Anion-Accelerated Amino-Cope Rearrangement Cascade Proposal

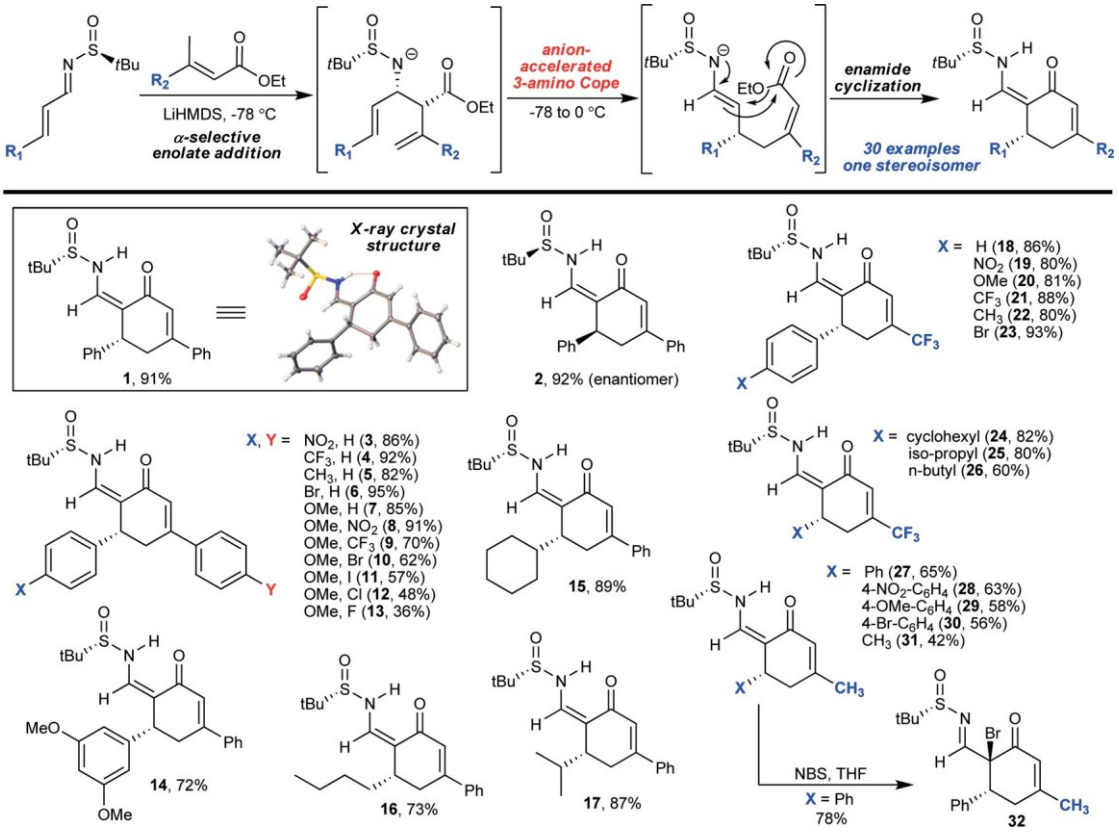


RESULTS AND DISCUSSION

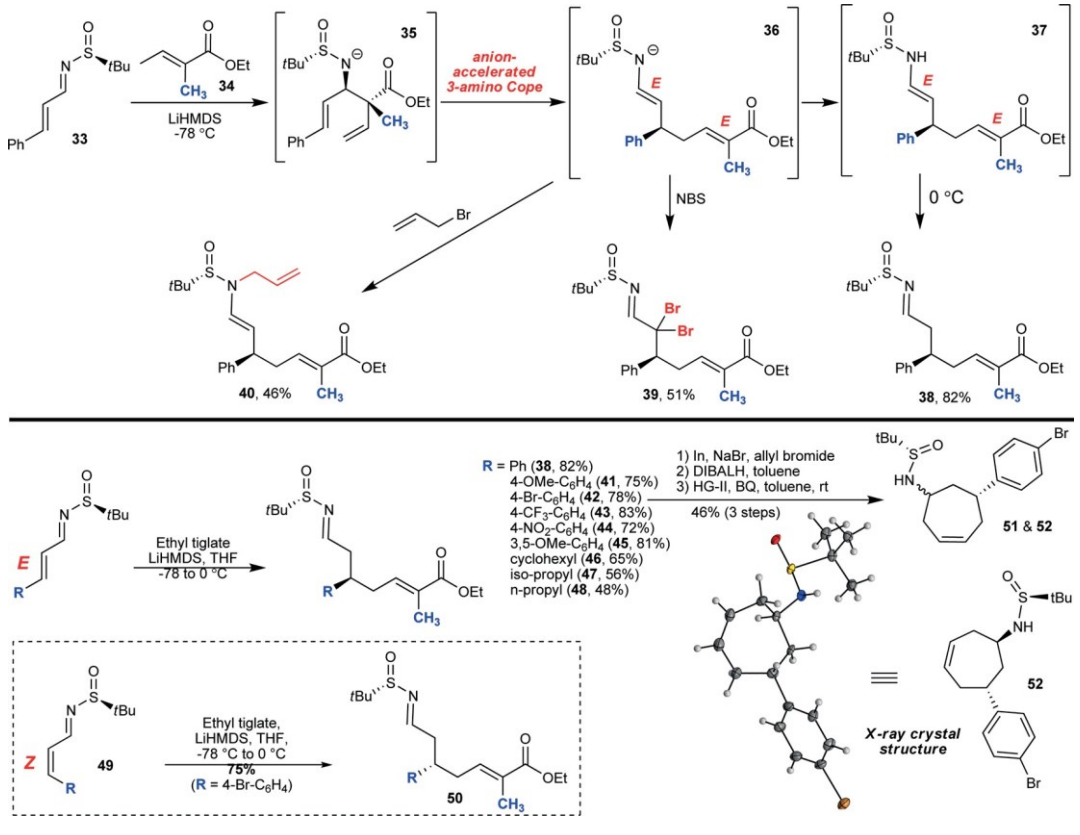
We have put the anion-accelerated amino-Cope rearrangement hypothesis to the test and are pleased to report that it has exceeded our most optimistic expectations (Scheme 4). When conjugated chiral imines are treated with lithium bis-(trimethylsilyl)amide (LiHMDS) in the presence of ethyl β-methyl cinnamate, at low temperature, selective enolate α-addition takes place immediately followed by the proposed anion-accelerated amino-Cope rearrangement upon slight warming of the reaction mixture. Unexpectedly, the anionic cascade proceeded to cleanly undergo an intramolecular *6-exo-trig* cyclization wherein the chiral enamide attacked a *Z*-enoate to form the six-membered ring products shown (Scheme 4) in excellent yields as single stereoisomers. Both aryl and alkyl imine substituents are tolerated. The nitrogen atom chiral auxiliary suppressed the previously deleterious competing [1,3]-rearrangement pathway, and regardless of the exact nature of the mechanism, the rearrangement proceeded without stereochemical erosion.[12] This new anion-accelerated amino-Cope rearrangement cascade affords complex chiral cyclohexenone products in high yields as single stereoisomers.[13] An X-ray crystal structure of one of the cyclization products (1) unambiguously established the overall structure and the absolute configuration of the newly formed stereocenter. An attractive practical application of this anion-accelerated amino-Cope rearrangement is its ability to provide ready access to either enantiomeric series (1 and 2). These examples represent the first useful asymmetric anion-accelerated amino-Cope rearrangement reaction. This new anionic reaction cascade is not limited to cinnamate nucleophiles (1−17). For example, ethyl 3,3-dimethyl acrylate and its trifluoromethyl derivative are also well-matched. The fluorinated nucleophile performs particularly well, affording chiral cyclohexenone products

DOI: 10.1021/jacs.7b07319
J. Am. Chem. Soc. 2017, 139, 13141−13146

Scheme 4. One-Pot Anion-Accelerated Amino-Cope Rearrangement Cascade

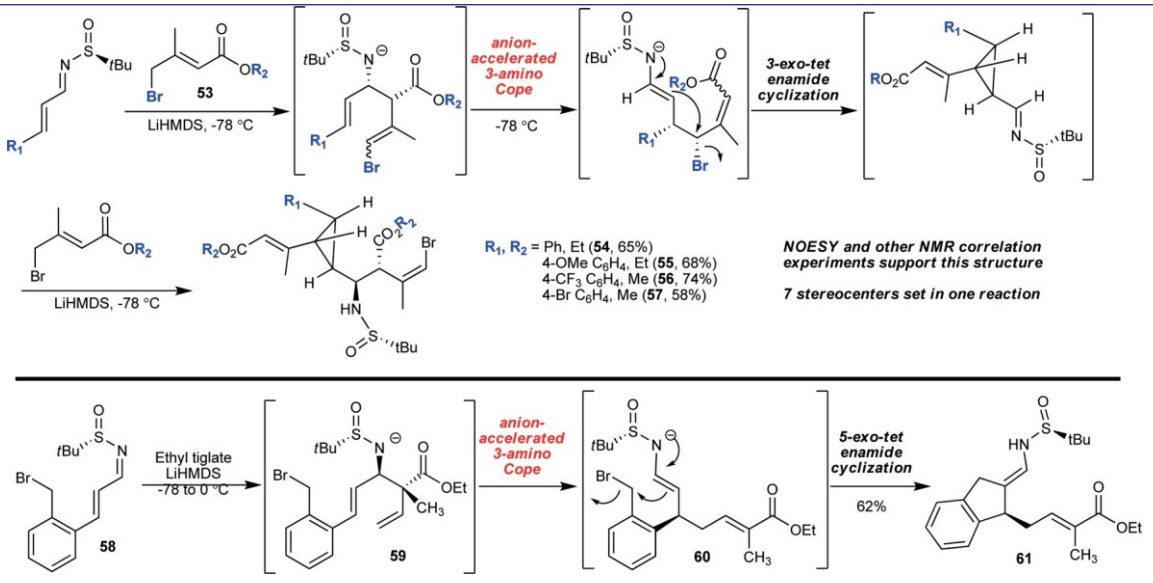


Scheme 5. Altering Nucleophile Substitution Diverts Anion-Accelerated Amino-Cope Rearrangement Cascade



DOI: 10.1021/jacs.7b07319
J. Am. Chem. Soc. 2017, 139, 13141−13146

Scheme 6. Alternative Enamide Cyclizations (3- and 5-*exo-tet*)



(18−26) decorated with a trifluoromethyl group in 60−82% yields. The success of this particular nucleophile is noteworthy given the importance of trifluoromethyl groups in drug discovery as evident from our recent pharmaceutical structure analysis.[14] Ethyl 3,3-dimethyl acrylate (27−31) also performs well, affording the chiral products in good to very good yields. When comparing the reactivity of the nucleophiles, we observe that the trifluoromethyl-substituted nucleophile (R_2 = CF_3) affords the rearrangement products more rapidly, at lower temperature, and in uniformly high yields. Aryl-substituted nucleophiles perform well with the methyl-substituted nucleophile being the slowest. The product enamide moiety has the potential to react in a variety of useful ways. For example, treatment with *N*-bromo succinimide (NBS) stereoselectively incorporates a bromine atom (32) in 78% yield.

We postulated that if the acrylate nucleophile was substituted with an α-substituent the enamide cyclization scenarios observed for the β-substituted nucleophile (Scheme 4) could be suppressed, thus opening the door for diverting the rearrangement toward formation of chiral acyclic products. Toward that end, when ethyl tiglate (34, Scheme 5) is employed as nucleophile, the anion-accelerated amino-Cope rearrangement proceeds at −78 °C to afford a product (37) wherein the resulting enoate is of the *E*- instead of *Z*-configuration, which shuts down cyclohexenone formation and affords an acyclic product instead. This promising reaction outcome creates opportunities for designing synthetic routes toward an incredible diversity of chiral acyclic products. Remarkably, we can isolate the intermediate enamine (37), which then readily converts to an imine (38). This has allowed us to confirm that both intermediate double bonds (enamine and enoate) are of *E*-configuration. The intermediate chiral enamide anion (36) can be trapped in situ with electrophiles. For example, exposure to allyl bromide results in exclusive *N*-allylation (40), while addition of an electrophilic bromide traps at carbon (39). Bromination affords exclusively an α,α-dibromo product. We have demonstrated this one-pot anionic cascade for nine *E*-conjugate imines (38 and 41−48), all of which afford chiral acyclic products[15] as single stereoisomer in generally excellent yields. When a *Z*-conjugated imine (49) is employed, a single stereoisomer of a product (50) with opposite configuration at the newly created stereocenter (R) is obtained.[16] In our original hypothesis (Scheme 3), we postulated that the anionic cascade could be pushed even further by adding a second nucleophile to the imine resulting from trapping of the intermediate enamide. This second in situ nucleophilic addition step would add another stereocenter, thus significantly increasing the complexity of the products. We have realized this reaction outcome as part of our efforts to unambiguously confirm the stereochemistry of the products presented in Scheme 5. Indium-mediated allylation of imine 42[17] and reduction of the resulting ester provided separable diastereomers of the amino alcohols (*dr* 3:1). Diene ring-closing metathesis reaction using second-generation Hoveyda-Grubbs (HG-II)[18] catalyst afforded cycloheptenes 51 and 52. Crystals of sufficient quality (52) enabled X-ray analysis, which surprisingly revealed that the absolute configuration of the newly formed stereocenter was opposite to that observed for β- substituted nucleophiles (Scheme 4).[19] The most plausible explanation for this outcome is that the initial nucleophilic attack onto the chiral imine proceeded from the opposite face.[20]

We were curious to learn how the intermediate enamide, which we have already demonstrated can undergo an in situ 6-*exo-trig* cyclization (Scheme 4) or be trapped in an intermolecular fashion (Scheme 5), would behave if presented with alternative cyclization choices. For this adventure, we postulated that γ-brominated 3,3-dimethyl acrylate (53) would present the intermediate rearrangement product (an enamide) with a competing *3-exo-tet* cyclization scenario. Treatment of the imines shown in Scheme 6 with the lithium enolate of 53 triggered an anionic cascade wherein the amino-Cope rearrangement proceeded at −78 °C followed by *3-exo-tet* cyclization to form a cyclopropane imine, which then further proceeded to react with the enolate again affording the products shown as single isomer (54−57).[21] Incredibly, seven stereocenters were established in this one-pot amino-Cope-enabled anionic cascade. Finally, to further highlight the wide range of cyclization pathways the intermediate chiral enamide offers, we designed a substrate (58) with a strategic leaving group being part of the imine instead of the nucleophile. Treatment of this substrate with ethyl tiglate proceeded as

DOI: 10.1021/jacs.7b07319
J. Am. Chem. Soc. 2017, 139, 13141−13146

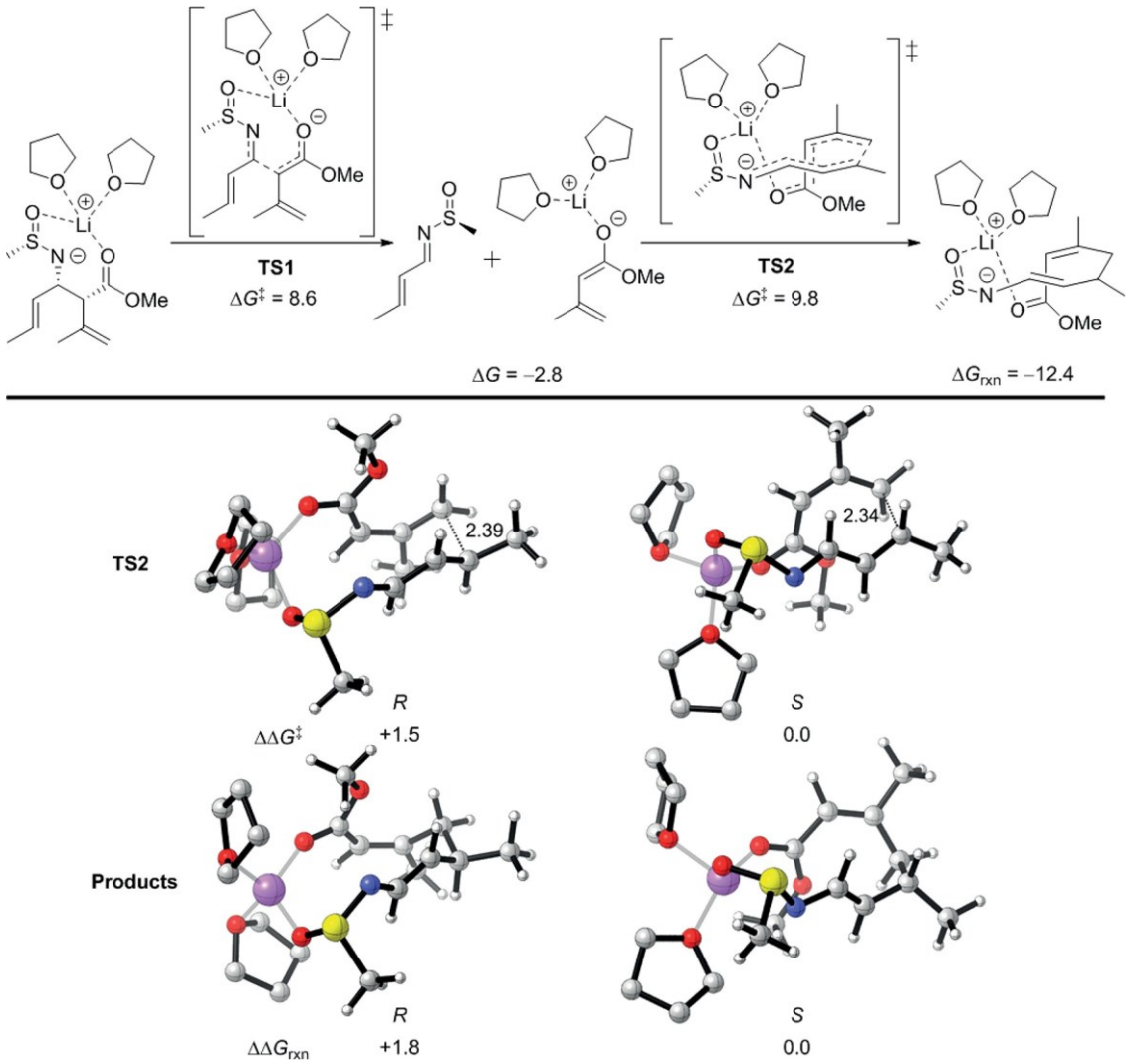


Figure 2. DFT-calculated mechanism of the anion-accelerated amino-Cope rearrangement. The structures of the recombination TS and the *R* and *S* products as shown. Distances and energies are given in units of Ångstroms and kcal mol^{-1}, respectively. Hydrogens on the THF solvent molecules were omitted for clarity.

expected with the anionic cascade being initiated with selective α-addition (59) followed by anion-accelerated amino-Cope rearrangement (60). We were excited to see that the enamide rearrangement product did indeed engage the benzylic bromide in a *5-exo-tet* cyclization as proposed to afford a chiral indane product (61) in very good yield.

Density functional theory (DFT) with the M06-2X functional and 6-311+G(d,p) basis set was employed to elucidate the mechanism of the amino-Cope rearrangement (Figure 2). The model includes a lithium counterion and two explicit THF solvent molecules as well as a polarizable continuum model for THF solvent.[22]

The favored mechanism was found to be a stepwise dissociative mechanism. The first step (TS1) in the rearrangement mechanism is the cleavage of the C_3–C_4 to form a lithium dienolate and sulfinylimine. The sulfinylimine can be formed as the *E*- (shown in Figure 2) or *Z*-imine; the *E*-imine is more stable by 5.0 kcal mol^{-1}. These fragments recombine in a chair transition state (TS2) to form the new carbon–carbon bond, which we calculate to have a slightly higher energy than TS1 by 1.2 kcal mol^{-1}. Additionally, there is a 1.5 kcal mol^{-1} preference for the transition structure that forms the observed *S*-product. The reaction is calculated to be exergonic for the formation of both product isomers, with a 1.8 kcal mol^{-1} (nearly 16:1 *S*/*R* product ratio) preference for the observed *S*-product. The origin of this preference arises from the conformation of the sulfinamide required to coordinate to the lithium counterion. In the *R* transition state, the sulfur and nitrogen atom lone pairs are *syn* to one another while in the *S* transition state they are *anti* to one another. The lone pair repulsion in the *R* transition state and product is also found in the corresponding conformers of the isolated imine (2.5 kcal mol^{-1}). A smaller lone pair repulsion on conformations has been observed in iminyl anions[23] and is well-known for peroxides and hydroxylamines. Our model shows that there is a kinetic and thermodynamic preference for the formation of the observed *S*-product due to the stereochemistry of the sulfinamide and the coordination geometry of the transition state (TS2).

CONCLUSIONS

In summary, we have developed useful new asymmetric anion-accelerated amino-Cope rearrangement reactions. A chiral sulfinamide nitrogen atom substituent ensures that the rearrangement is stereoselective and high yielding. This same

DOI: 10.1021/jacs.7b07319
J. Am. Chem. Soc. 2017, 139, 13141–13146

chiral auxiliary enables assembly of the amino-Cope substrate in situ and imparts its influence on both the enamide rearrangement product and the resulting chiral imine. We have demonstrated that this amino-Cope enabled anionic cascade can be controlled to afford either chiral cyclic or acyclic products by use of appropriate nucleophiles and electrophiles. The possibilities for programming this fertile new anionic cascade for synthetic target purposes seem plentiful. Our efforts are currently focused on further deciphering the stepwise dissociation−recombination reaction mechanism as well as investigating and applying this new asymmetric anion-accelerated amino-Cope rearrangement cascade.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07319.

Experimental procedures and characterization data for all new compounds as well as computational methods (PDF)
Crystallographic data for 1 (CCDC 1451254) (CIF)
Crystallographic data for 52 (CCDC 1556649) (CIF)

AUTHOR INFORMATION

Corresponding Authors

*houk@chem.ucla.edu

*njardars@email.arizona.edu

ORCID

K. N. Houk: 0000-0002-8387-5261

Jon T. Njardarson: 0000-0003-2268-1479

Author Contributions

I.C. and P.D contributed equally to the creation of this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-1266365 to J.T.N. and CHE-1361104 to K.N.H.) for financial support of this research. We are grateful for the computational resources provided by UCLA Institute for Digital Research and Education and the National Science Foundation through XSEDE Science Gateways Program (TG-CHE040013N).

REFERENCES

(1) (a) Berson, J. A.; Jones, M. J. *J. Am. Chem. Soc.* 1964, *86*, 5019. (b) Wilson, S. R. *Org. React.* 1993, *43*, 93.

(2) (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* 1975, *97*, 4765. (b) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* 1978, *100*, 2242. (c) Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* 1979, *101*, 1994.

(3) (a) Paquette, L. A. *Tetrahedron* 1997, *53*, 13971. (b) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* 1990, *29*, 609. (c) Haffner, F.; Houk, K. N.; Reddy, Y. R.; Paquette, L. A. *J. Am. Chem. Soc.* 1999, *121*, 11880.

(4) (a) Stogryn, E. L.; Brois, S. J. *J. Org. Chem.* 1965, *30*, 88. (b) Wender, P. A.; Schaus, J. M.; Torney, D. C. *Tetrahedron Lett.* 1979, *20*, 2485. (c) Jemison, R. W.; Ollis, D. W.; Sutherland, I. O.; Tannock, J. *J. Chem. Soc., Perkin Trans. 1* 1980, *7*, 1462. (d) Dollinger, M.; Henning, W.; Kirmse, W. *Chem. Ber.* 1982, *115*, 2309.

(5) (a) Sprules, T. J.; Galpin, J. D.; Macdonald, D. *Tetrahedron Lett.* 1993, *34*, 247. (b) Dobson, H. K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T. R.; Macdonald, D. *Tetrahedron Lett.* 1999, *40*, 3119.

(6) (a) Yoo, H. Y.; Houk, K. N.; Lee, J. K.; Scialdone, M. A.; Meyers, A. I. *J. Am. Chem. Soc.* 1998, *120*, 205. (b) Haeffner, F.; Houk, K. N.; Schulze, S. M.; Lee, J. K. *J. Org. Chem.* 2003, *68*, 2310.

(7) (a) Allin, S. M.; Button, M. A. C. *Tetrahedron Lett.* 1998, *39*, 3345. (b) Allin, S. M.; Button, M. A. C.; Baird, R. D. *Synlett* 1998, *1998*, 1117. (c) Allin, S. M.; Button, M. A. C. *Tetrahedron Lett.* 1999, *40*, 3801. (d) Allin, S. M.; Baird, R. D.; Lins, R. J. *Tetrahedron Lett.* 2002, *43*, 4195. (e) Allin, S. M.; Essat, M.; Horro-Pita, C. H.; Baird, R. D.; McKee, V.; Elsegood, M.; Edgar, M.; Andrews, D. M.; Shah, P.; Aspinall, I. *Org. Biomol. Chem.* 2005, *3*, 809.

(8) Allin, S. M.; Horro-Pita, C.; Essat, M.; Aspinall, I.; Shah, P. *Synth. Commun.* 2010, *40*, 2696.

(9) Chogii, I.; Njardarson, J. T. *Angew. Chem., Int. Ed.* 2015, *54*, 13706.

(10) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* 2010, *110*, 3600.

(11) Su, X.; Zhou, W.; Li, Y.; Zhang, J. *Angew. Chem., Int. Ed.* 2015, *54*, 6874.

(12) The initial α-enolate imine adducts can be isolated at low temperature and resubjected to alternative bases. Our preliminary investigations have revealed that Na and Li counterions (generated from treating the amino alcohol adduct with LiHMDS, NaH, BuLi, or NaHMDS) are critical for the success of the rearrangement while K is detrimental. This suggests that the Na and Li counterions are playing a key role, most likely by suppressing the dissociations that plagued earlier investigations.

(13) Interestingly, when the imine is unsubstituted, two products are obtained in a 2:1 ratio in 86% yield. The minor product is the [3,3]-rearrangement product and major is the [1,3]-rearrangement product (2:1 *dr*).

(14) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* 2014, *57*, 2832.

(15) Protonation of the intermediate enamine results in *E*/*Z*-imine product mixtures, which result in a single compound when reduced with $NaBH_4$.

(16) To further confirm this result, we have separately reduced the imines of 42 and 50 and then oxidized the chiral auxiliary of the resulting product to its Bus-substituted amine to afford products that are enantiomeric as evident from optical rotation measurements (see Supporting Information, Scheme S5B, S52).

(17) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* 2008, *10*, 1259.

(18) (a) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* 2005, *127*, 17160. (b) Cho, J. H.; Kim, B. M. *Org. Lett.* 2003, *5*, 531.

(19) This stereochemical assignment has been further validated by subjecting a common chiral imine separately to the ethyl esters of β-methyl (Scheme S5C, Part A, S56) and α-methyl (Scheme S5C Part B, S61) crotonate and then chemically converting the resulting amino-Cope rearrangement products to a common chiral structure. Chemical characterization revealed that these products were identical in all respects (NMR, IR, mass-spec) but had opposite optical rotation values (see Supporting Information).

(20) The main competing pathway for this new class of anionic cascades is a retro-Mannich reaction (Davis, F. A.; Zhang, Y.; Qiu, H. *Org. Lett.* 2007, *9*, 833). It is plausible that the α-substituted nucleophiles add from the same face as the nucleophiles in Scheme 4 but then fail to undergo the rearrangement and instead undergo a retro-Mannich reaction before then adding from the opposite face and rearranging..

(21) Maintaining the reaction temperature at −78 °C is critical for success.

(22) Essafi, S.; Tomasi, S.; Aggarwal, V. K.; Harvey, J. N. *J. Org. Chem.* 2014, *79*, 12148.

(23) Zhang, H.; Wu, W.; Ahmed, B. M.; Mezei, G.; Mo, Y. *Chem. - Eur. J.* 2016, *22*, 7415.

DOI: 10.1021/jacs.7b07319
J. Am. Chem. Soc. 2017, 139, 13141−13146