OL Organic Letters

pubs.acs.org/OrgLett Letter

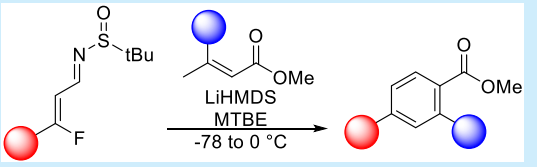
Anionic Amino-Cope Rearrangement Cascade Synthesis of 2,4-Substituted Benzoate Esters from Acyclic Building Blocks

M. Haziq Qureshi and Jon T. Njardarson*

Cite This: https://doi.org/10.1021/acs.orglett.2c03134 Read Online

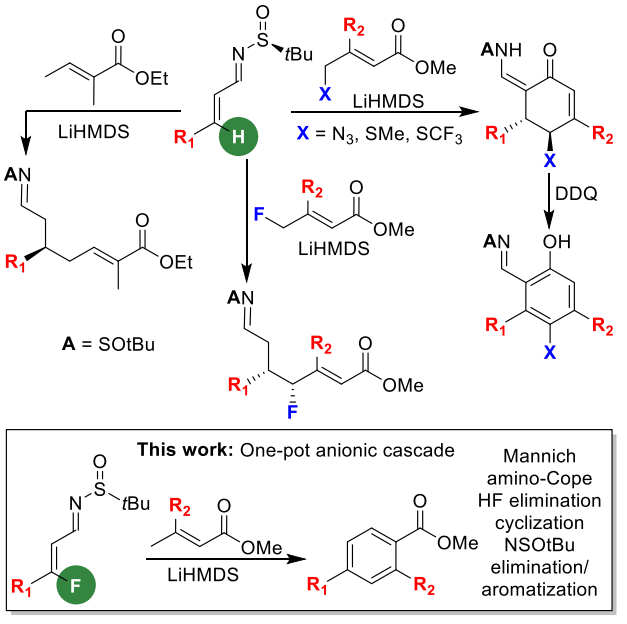
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We report a new anionic cascade for assembling 2,4-substituted benzoate esters in one pot from racemic β-fluoro-substituted conjugated *tert*-butylsulfinyl imines and 3-substituted methyl 2-butenoates. Dienolate formation triggers a Mannich addition followed by an amino-Cope like rearrangement, which results in immediate elimination of fluoride by a lithiated enamine. The newly formed 1,4-diene intermediate contains a highly acidic proton which is spontaneously deprotonated, leading to a facile intramolecular cyclization followed by sulfinamide group elimination and aromatization.



In 2017, our group initiated a new chapter in the neglected area of anionic amino-Cope chemistry,[1−5] wherein we demonstrated that chiral conjugated sulfinyl imines reacted with lithium dienolates via an initial Mannich addition followed by an anionic amino-Cope rearrangement to form either cyclic or acyclic products depending on the substitution of the starting butenoate (Scheme 1).[6] For example, β-substituted dienolates afforded cyclohexenone products while α-substituted dienolates yielded an acyclic product, which interestingly was observed to have the opposite configuration at the newly formed stereocenter. We have since demonstrated how the cyclohexenone products formed from the amino-Cope rearrangement can be converted to phenols and arenes upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), representing an expedient two-step annulation route to densely substituted aromatic products from simple acyclic precursors.[7] Most recently, we have demonstrated that γ-heteroatom substituted dienolates can be employed in the anionic amino-Cope reaction platform to form cyclic and acyclic products with two new stereocenters, with the configuration of new stereocenters strongly dependent on the nature of the heteroatom substituent.[8] In exploring β-fluoro-substituted sulfinyl imines as amino-Cope reaction partners, we uncovered a remarkable new anionic cascade that forms 2,4-substituted benzoate esters in one pot when engaged with dienolates.

Scheme 1. Njardarson Group Anionic Amino-Cope Rearrangement Platform: New Anionic Annulation Cascade



As part of realizing the full potential of this new amino-Cope platform, we initially set out to explore if a quaternary stereocenter could be installed by employing conjugated sulfinyl imines with two β-substituents. Our studies quickly revealed that the formation of an all-carbon quaternary center was not feasible using this approach, as Mannich adducts did not proceed along the amino-Cope reaction pathway.

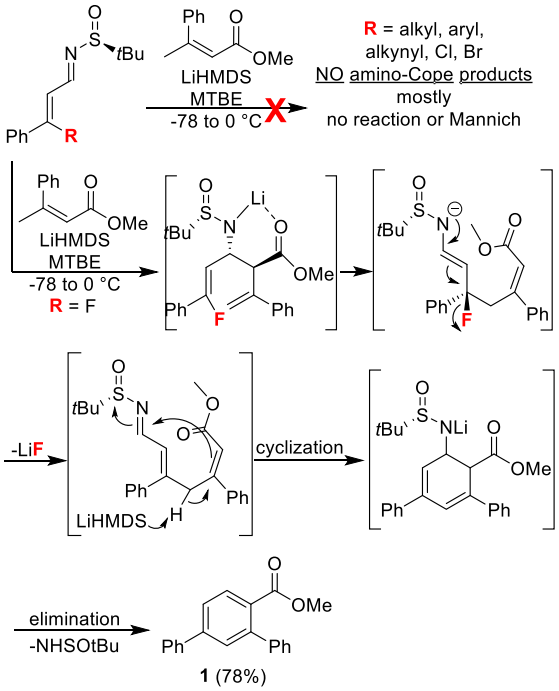
We therefore turned our attention to small sulfinyl imine β-heteroatom substituents to assess if any second β-substituent, beyond hydrogen, could be accommodated in the amino-Cope rearrangement cascade. Halogens emerged as an attractive β-sulfinyl imine substituent series to study, as halogens vary in

Received: September 14, 2022

https://doi.org/10.1021/acs.orglett.2c03134
Org. Lett. XXXX, XXX, XXX−XXX

size and the starting β-bromo and β-chloro substituted imines could be assembled rapidly in two steps from acetophenone via a Vilsmeier−Haack reaction followed by imine formation. These studies revealed that β-bromo- and β-chloro-substituted imines did not afford any amino-Cope products but instead primarily afforded Mannich addition products. In contrast, when a β-fluoro-substituted sulfinyl imine was employed, a new product identified as 2,4-diphenyl methyl benzoate was formed in high yield (**1**, Scheme 2). With fluorine being barely

Scheme 2. Discovery of a New Amino-Cope Rearrangement Centered Anionic Cascade

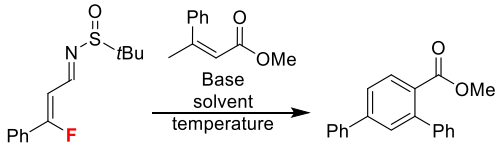


larger than a hydrogen atom, it is not surprising that a fluorine atom, which is significantly smaller in size than the other halogens, was shown to be compatible with the amino-Cope reaction cascade. We tentatively propose that following an initial reversible Mannich addition, indeed, an amino-Cope rearrangement proceeds, followed by a rapid elimination of fluorine instead of a cyclization as observed previously. The resulting diene product contains very acidic hydrogen atoms, which are then immediately deprotonated, setting the stage for an intramolecular addition of an ester enolate to the sulfinyl imine followed by a facile aromatization via elimination of NHSOtBu.

Following discovery of this new anionic cascade the remainder of our investigations proceeded with *racemic* imines. Anionic cascade optimization insights are detailed in Table 1, which were guided by solvent and temperature observations established as critical in our earlier anionic amino-Cope studies. The ethereal solvent tetrahydrofuran (THF), methyl *tert*-butyl ether (MTBE), and cyclopentyl methyl ether (CPME) were all shown to be compatible, with MTBE demonstrating a consistently marginal advantage (Table 1, entries 1−3), which is consistent with what we observed in our most recent amino-Cope studies. Use of at least 2 equiv of lithium bis(trimethylsilyl)amide (LiHMDS) was deemed critical with 2.2 equiv being most suitable. We also learned that, with respect to temperature, it was sufficient to run the reaction first for 2 h at −78 °C compared to the 8 h reaction times we had used in our previous studies. The reaction was then warmed to 0 °C, and it was observed that it was important to hold the temperature at 0 °C for a minimum of 30 min before quenching to obtain optimal yields (entry 5). Interestingly, both sodium bis(trimethylsilyl)amide (NaHMDS) and potassium bis(trimethylsilyl)amide (KHMDS) were shown to facilitate the cascade, albeit in lower 62% (entry 8) and 51% yield (entry 9), respectively. Use of potassium *tert*-butoxide resulted in no formation of annulation product but instead ester transesterification and addition of the resulting methoxide ion to the β-fluoro imine to form a β-methoxy imine in high yield. Use of *n*-butyllithium did not yield any desired product, but only resulted in an addition to the imine.

All β-fluoro imines used in our studies were synthesized using the three-step route outlined in Scheme 3. It is worth noting that β-fluoro-conjugated imines are rare,[9] with no reported *tert*-butylsulfinyl imines. Readily available acetophe-

Table 1. Optimization of Anionic Annulation Cascade

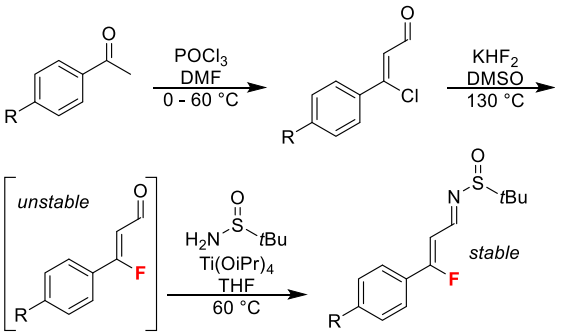


entry	base (equiv)	solvent (temp)	reaction time[a] (h)	isolated yield (%)
1	LiHMDS (2 equiv)	THF (−78 then 0 °C)	8 h then 30 min	68
2	LiHMDS (2 equiv)	MTBE (−78 then 0 °C)	8 h then 30 min	72
3	LiHMDS (2 equiv)	CPME (−78 then 0 °C)	8 h then 30 min	69
4	LiHMDS (2.2 equiv)	MTBE (0 °C)	8 h then 30 min	54
5	LiHMDS (2.2 equiv)	MTBE (−78 then 0 °C)	2 h then 30 min	**78**
6	LiHMDS (2.2 equiv)	MTBE (−78 then 0 °C)	2 h then 10 min	61
7	LiHMDS (2.2 equiv)	MTBE (−78 then 0 °C)	8 h then 10 min	64
8	NaHMDS (2.2 equiv)	MTBE (−78 then 0 °C)	2 h then 30 min	62
9	KHMDS (2.2 equiv)	MTBE (−78 then 0 °C)	2 h then 30 min	51
10	KOtBu (2.2 equiv)	tBuOH (−78 then 0 °C)	2 h then 30 min	0
11	*n*-BuLi (2.2 equiv)	MTBE (−78 then 0 °C)	2 h then 30 min	0

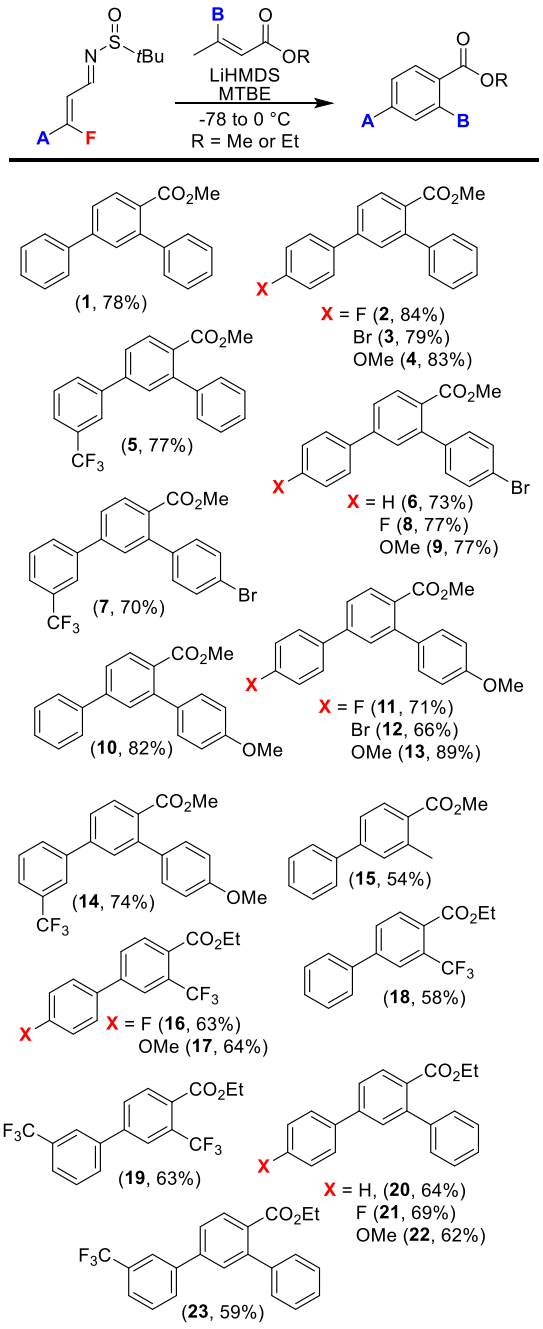
[a]The two reaction time numbers refer to total reaction times at −78 °C (first number) and 0 °C (second number).

https://doi.org/10.1021/acs.orglett.2c03134
Org. Lett. XXXX, XXX, XXX−XXX

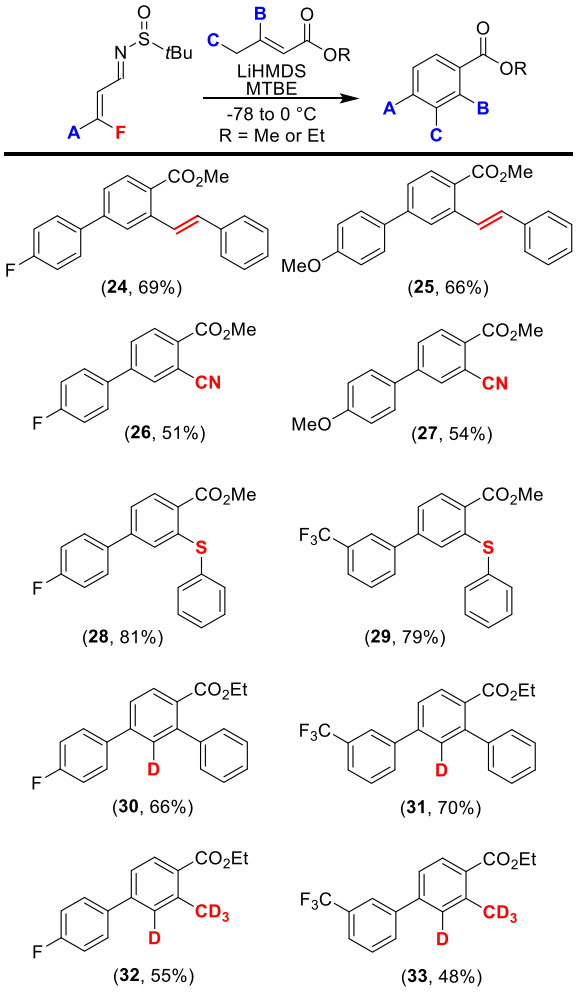
Scheme 3. Synthesis of β-Fluoro Sulfinyl Imines



Scheme 4. Scope of Anionic Cascade for Enoates with β-Aryl, $-CH_3$, and $-CF_3$ Substituents



Scheme 5. Scope of Anionic Cascade for Designer Enoates with Functional Groups

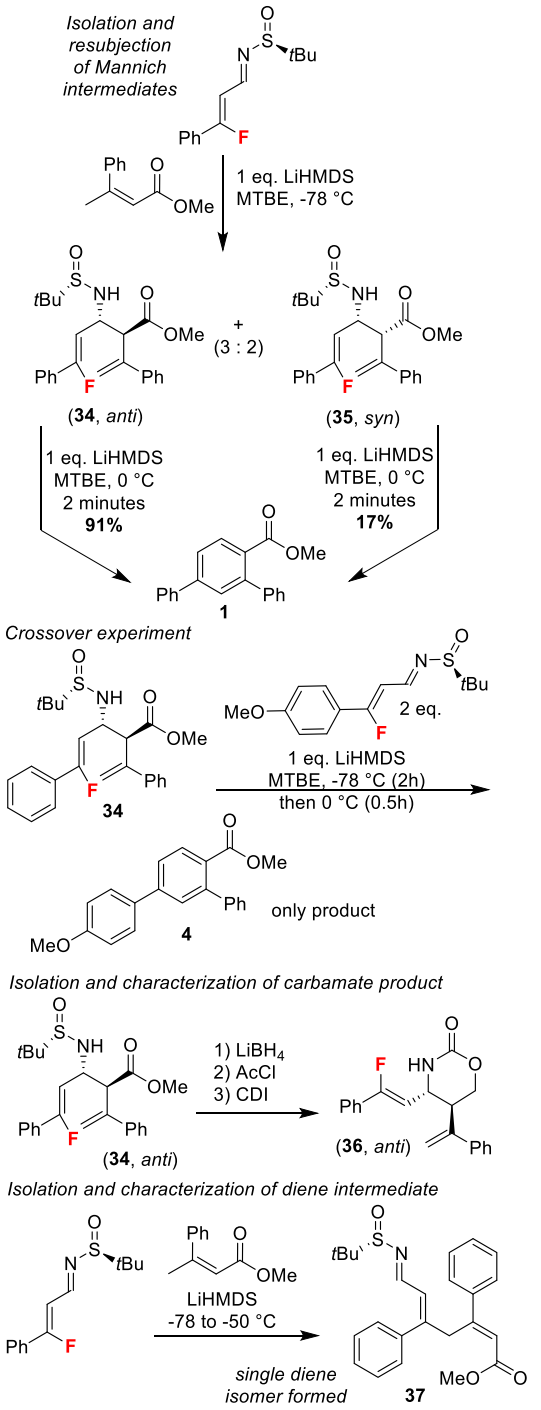


none derivatives were first subjected to Vilsmeier–Haack conditions to form β-chloro enal products,[10] which were then treated with a cheap and stable fluoride source in the form of potassium hydrogen fluoride (KHF_2) following the procedure of Sun and Gong to afford β-fluoro enal products.[11] We quickly learned that the β-fluoro enals were quite unstable, and in our optimized procedure we immediately converted crude β-fluoro enals to the desired β-fluoro *tert*-butylsulfinyl imines, which were shown to be very stable.

We next turned our attention to explore the scope of this new amino-Cope enabled anionic cascade. These results are presented in Scheme 4 with 23 examples highlighting the use of enoate nucleophiles substituted with β-aryl, -methyl, and -trifluoromethyl groups. Methyl ester enoates containing β-aryl groups perform quite well with yields ranging from 72 to 84% (**1**–**14**) with very little difference in yield between electron-rich or electron-poor aryl groups. 3,3-Dimethyl ethyl butanoate (β-methyl) does work (**15**), with a substantially lower yield of 54%. Interestingly, the corresponding trifluoromethyl enoate nucleophiles perform noticeably better (**16**–**19**) than their methyl counterparts despite being ethyl esters, delivering the annulation products in 58–64% yield. As we have observed in our earlier amino-Cope studies, improved yields were obtained with methyl ester enoates compared to ethyl ester enoates,

https://doi.org/10.1021/acs.orglett.2c03134
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 6. Anionic Cascade Control Experiments



with yields for the ethyl ester enoates ranging from 59 to 69% (**20**−**23**).

Shown in Scheme 5 are applications of this new anionic cascade with enoate nucleophiles containing useful functional group handles. A styrenyl group can be incorporated quite efficiently to afford cascade products in 69% (**24**) and 66% yield (**25**). Nitriles, which are among the most versatile small functional groups serving as gateways to a variety of carbonyls and high value amine groups, are demonstrated to be compatible substituents (**26** and **27**). Excitingly, enoates containing a β-phenylthio group work phenomenally well, affording the desired 2-phenylthio benzoate products in 81% (**28**) and 79% yield (**29**). Deuteration has emerged as substitution strategy of high value in the pharmaceutical industry,[12] which has gathered increased attention and focus following the approval of deutetrabenazine as treatment for chorea associated with Huntington's disease and the recent approval of deucravacitinib[13] for the treatment of plaque psoriasis. Earlier this year, Professor Beller and his team summarized recent advances in deuteration of organic molecules.[14] Toward that end, we have demonstrated how this new cascade can be utilized to access high value selectively deuterated products (**30**−**33**) that would be challenging to efficiently access using other methods. Importantly, this deuteration strategy enabled us to also access 2,3,4-substituted benzoates (**30**−**33**).

Key mechanistic control experiments are presented in Scheme 6. By running the reaction at low temperature for a short time we can isolate two Mannich products in a 2:1 ratio, which NMR analysis (see the Supporting Information) revealed to be *anti*-isomer **34** and *syn*-isomer **35**. The *anti* stereochemistry of **34** was confirmed by conversion to the rigid cyclic carbamate **36** and subsequent rigorous NMR analysis. Most interestingly, when the two Mannich isomers are resubjected to the base at 0 °C for a short time (2 min), the *anti*-isomer **34** proceeds completely to the product (**2**), while the *syn*-isomer **35** only formed 17% of the product along with imine formation via a retro-Mannich; a testament to the reversibility of the reaction and an indication that the *anti*-diastereomer is the matched isomer for the cascade. This reversibility is further confirmed convincingly via crossover experiment, wherein Mannich adduct **34** is treated with base in the presence of 2 equiv of methoxyimine, which we had demonstrated was faster reacting in the Mannich addition, resulting in exclusive formation of the methoxy-substituted product (**4**). Furthermore, by carefully controlling the reaction time at low temperature we can isolate the 1,4-diene intermediate (**37**) as a single isomer.

In conclusion, we have uncovered a new anionic annulation cascade enabled by the union of conjugated β-fluoro *tert*-butylsulfinyl imines and lithium dienolates. The cascade is initiated by a Mannich addition followed by an amino-Cope rearrangement step producing a lithium enamide, which immediately eliminates fluoride to form a diene, which proceeds to be deprotonated, undergoing cyclization and aromatization to form the benzoate annulation products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03134.

Experimental procedures and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jon T. Njardarson − *Department of Chemistry and Biochemistry, University of Arizona, Tucson, Arizona 85721, United States;* orcid.org/0000-0003-2268-1479; Email: njardars@arizona.edu

https://doi.org/10.1021/acs.orglett.2c03134
Org. Lett. XXXX, XXX, XXX−XXX

Author

M. Haziq Qureshi − *Department of Chemistry and Biochemistry, University of Arizona, Tucson, Arizona 85721, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c03134

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank the National Science Foundation (CHE-1855708 and CHE-2153657) for financial support of this research program and for supporting the purchase of an NMR spectrometer (MRI-grant CHE-1920234) and a single-crystal X-ray diffractometer (MRI-grant CHE-2117516). We are most grateful to Nicholas R. Lauta (Department of Chemistry and Biochemistry, University of Arizona) for the synthesis of the phenylthio-substituted nucleophile and to Dr. Vlad Kumirov (Department of Chemistry and Biochemistry, University of Arizona) with his assistance in determining the stereochemistry of the intermediate compounds in the cascade.

■ REFERENCES

(1) Spules, T. J.; Galpin, J. D.; Macdonald, D. Charge-accelerated Cope rearrangements of 3-amino-1,5-dienes. *Tetrahedron Lett.* **1993**, *34*, 247−250.

(2) Allin, S. M.; Button, M. A. C. The first example of asymmetric induction in an anionic amino-Cope rearrangement. *Tetrahedron Lett.* **1998**, *39*, 3345−3348.

(3) Yoo, H. Y.; Houk, K. N.; Lee, J. K.; Scialdone, M. A.; Meyers, A. I. New paradigm for anionic heteroatom Cope rearrangements. *J. Am. Chem. Soc.* **1998**, *120*, 205−206.

(4) Dobson, H. K.; LeBlanc, R.; Perrier, H.; Stephenson, C.; Welch, T. R.; Macdonald, D. [1,3] and [3,3] Rearrangements of 3-amino-1,5-hexadienes: Solvent effect on the regioselectivity. *Tetrahedron Lett.* **1999**, *40*, 3119−3122.

(5) Allin, S. M.; Button, M. A. C. Evidence for alternative mechanisms in the amino-Cope rearrangement. *Tetrahedron Lett.* **1999**, *40*, 3801−3802.

(6) Chogii, I.; Das, P.; Fell, J. S.; Scott, K. A.; Crawford, M. N.; Houk, K. N.; Njardarson, J. T. New Class of Anion-Accelerated Amino-Cope Rearrangements as Gateway to Diverse Chiral Structures. *J. Am. Chem. Soc.* **2017**, *139*, 13141−13146.

(7) Scott, K. A.; Groch, J. R.; Chogii, I.; Delost, M. D.; Das, P.; Njardarson, J. T. Dienolate Annulation Approach for Assembly of Densely Substituted Aromatic Architectures. *J. Org. Chem.* **2021**, *86*, 10555−10567.

(8) Das, P.; Delost, M. D.; Qureshi, M. H.; Bao, J.; Fell, J. S.; Houk, K. N.; Njardarson, J. T. Dramatic Effect of g-Heteroatom Dienolate Substituents on Counterion Assisted Asymmetric Anionic Amino-Cope Reaction Cascades. *J. Am. Chem. Soc.* **2021**, *143*, 5793−5804.

(9) Zentner, C. A.; Anson, F.; Thayumanavan, S.; Swager, T. M. Dynamic Imine Chemistry at Complex Double Emulsion Interfaces. *J. Am. Chem. Soc.* **2019**, *141*, 18048−18055.

(10) Yang, Z.; Lu, N.; Wei, Z.; Cao, J.; Liang, D.; Duan, H.; Lin, Y. Base-Promoted Intermolecular Cyclization of Substituted 3-Aryl-(Heteroaryl)-3-chloroacrylaldehydes and Tetrahydroisoquinolines: An Approach to Access Pyrrolo[2,1-a]isoquinolines. *J. Org. Chem.* **2016**, *81*, 11950−11955.

(11) Zhang, J.; Liu, L.; Duan, J.; Gu, L.; Chen, B.; Sun, T.; Gong, Y. Stereoselective One-Pot Sequential Dehydrochlorination/trans-Hydrofluorination Reaction of b-Chloro-a,b-Unsaturated Aldehydes and Ketones: Facile Access to (Z)-b-Fluoro-b-Arylenals/b-Fluoro-b-Arylenones. *Adv. Synth. Catal.* **2017**, *359*, 4348−4358.

(12) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. Applications of Deuterium in Medicinal Chemistry. *J. Med. Chem.* **2019**, *62*, 5276−5297.

(13) Treitler, D.; Soumeillant, M.; Simmons, E.; Lin, D.; Inankur, B.; Rogers, A.; Dummeldinger, M.; Kolotuchin, S.; Chan, C.; Li, J.; Freitag, A.; Gonzalez, F.; Smith, M.; Sfouggatakis, C.; Wang, J.; Benkovics, T.; Deerberg, J.; Simpson, J.; Chen, K.; Tymonko, S. Development of a Commercial Process for Deucravacitinib, a Deuterated API for TYK2 Inhibition. *Org. Process Res. Dev.* **2022**, *26*, 1202−1222.

(14) Kopf, S.; Bourriquen, F.; Li, W.; Neumann, H.; Junge, K.; Beller, M. Recent Developments for the Deuterium and Tritium Labeling of Organic Molecules. *Chem. Rev.* **2022**, *122*, 6634−6718.