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Strategic Vinyl Sulfone Nucleophile β-Substitution Significantly Impacts Selectivity in Vinylogous Darzens and Aza-Darzens Reactions

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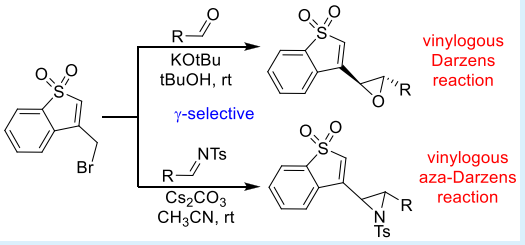
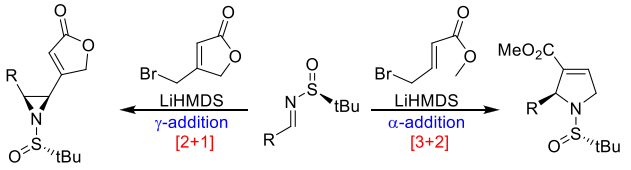
ABSTRACT: Vinylogous Darzens and aza-Darzens reactions employing a benzothiophene 1,1-dioxide nucleophile are reported. These new [2 + 1] annulation reactions, which proceed under mild reaction conditions, are γ-selective, affording *trans*-epoxides selectively and favoring *trans*-aziridines. The reactions are base-dependent, with KOtBu and Cs_2CO_3 being optimal for aldehyde and imine annulations, respectively. Comparison of the benzothiophene nucleophile to its acyclic counterpart reveals superior performance in the case of aldehydes, while the outcome varies depending on the sulfonamide imine used.



Our group's continued interest in copper-catalyzed ring expansions of vinyl oxiranes and aziridines[1] has focused our attention on identifying reliable and efficient methods for their assembly. We have found [2 + 1] anionic annulations such as the Corey−Chaykovsky[2] and Darzens[3] reactions, which assemble oxirane and aziridine rings in one pot from simple precursors, to best support our synthetic goals.[4] As part of our efforts to secure access to chiral nitrogen heterocycles, we have turned our attention to exploring the potential of the relatively neglected vinylogous asymmetric aza-Darzens reaction. Our recent studies have revealed remarkable substituent dependence (Scheme 1), wherein unsubstituted 4-

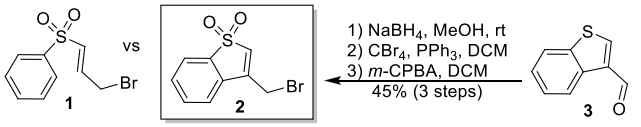
Scheme 1. Dramatic Dienolate Substituent Effects in Aza-Darzens-Inspired Annulations



bromocrotonate nucleophiles add in an α-fashion to afford 3-pyrrolines[5] while β-substituted crotonates add from the dienolate γ-position to afford vinyl aziridines.[6]

These unexpected substituent effects, coupled with our general interest in expanding investigations of this underexplored class of vinylogous Darzens-type annulations, prompted us to evaluate sulfones as electron-withdrawing-group replacements for carboxylates. Sulfones are among the most versatile functional groups in organic synthesis. Their unique transformation capabilities include participation in a plethora of "traceless" reactions wherein the sulfone group is replaced by carbon or a heteroatom via anionic, radical, or metal-mediated processes. Motivated by the different dienolate addition outcomes, we decided to evaluate and contrast the annulation behaviors of 4-bromo-substituted vinyl sulfones **1** and **2** toward aldehyde and imine electrophiles (Scheme 2). We were

Scheme 2. Cyclic and Acyclic 4-Bromo-Substituted Vinyl Sulfones



encouraged by a single report by Gallaghern and Grayson,[7] who established that with butyllithium Darzens reactions with **1** could be realized for a handful of aldehydes but did not explore imines toward the formation of aza-Darzens products. We initiated our efforts by improving the synthesis of **2**,[8] whose resulting carbanion has not been employed previously as a nucleophile and this study aims to showcase in additions to aldehyde and imine electrophiles.

We decided to first explore the Darzens reaction performance differences for **1** and **2** (Scheme 3). Toward that end, we developed a mild procedure employing potassium *tert*-butoxide

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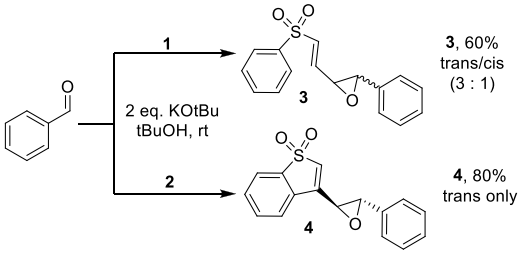
Scheme 3. Darzens Annulations with Vinyl Sulfones 1 and 2



(KOtBu) in *tert*-butanol at room temperature. The addition order is critical, and it is essential that the base be added last and slowly (over 1 h). In contrast, if the nucleophile is added last, the yield craters to nearly zero. Both **1** and **2** add in a γ-selective fashion to benzaldehyde, delivering the expected epoxide Darzens products (**3** and **4**) in 60% and 80% isolated yield, respectively. There are key significant differences, such as higher yields and complete *trans* selectivity in the case of **2**, but more importantly, as we expanded our investigations to other aldehydes, **2** continued to shine (Scheme 4) while **1** delivered abysmal results.

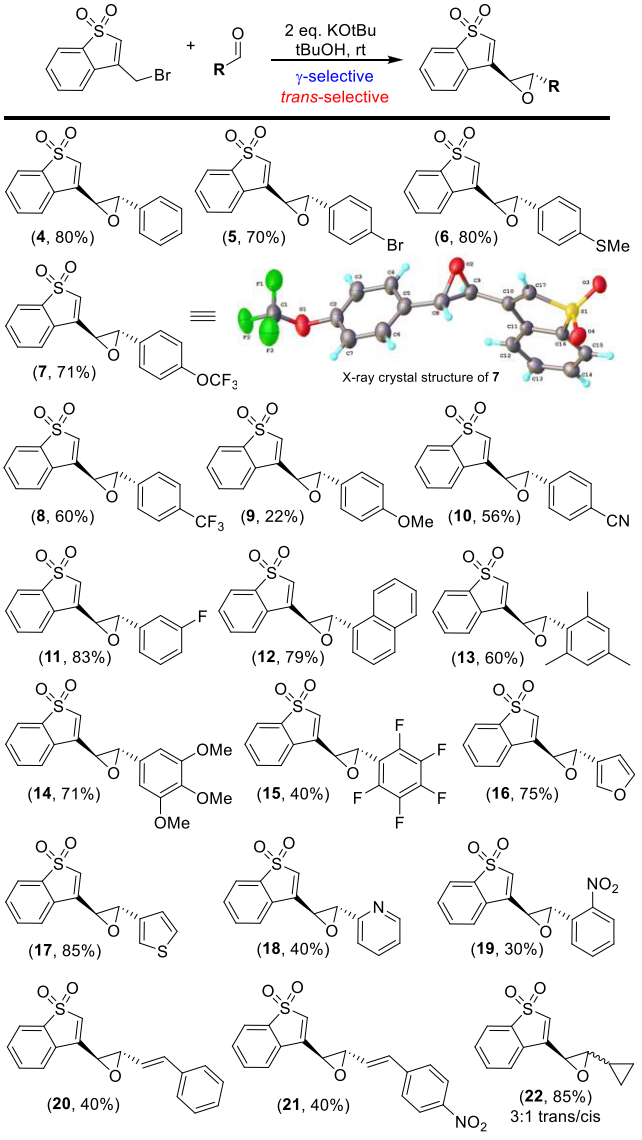
The scope of this new vinylogous Darzens reaction for **2** is presented in Scheme 4, with 19 examples, including an X-ray crystal structure confirmation for **7**.[9] Not surprisingly in view of the reaction conditions, aromatic aldehydes are the best-suited partners for the annulation, as they do not suffer from competing aldehyde self-condensation pathways. The yields of diverse *trans*-epoxide products range from good to excellent.

We propose steric hindrance to be the major driving force favoring *trans*-epoxide formation (Scheme 5). Both *syn*- and *anti*-addition intermediates are generated, which in the case of the *anti* addition proceed to undergo 3-*exo*-*tet* cyclization, while for the *syn*-addition intermediates a sterically unfavorable cyclization transition state results in a retro-aldol reaction path.

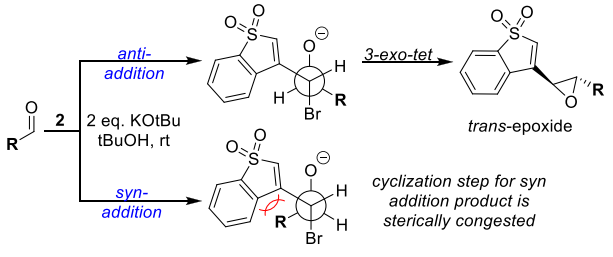
The epoxides resulting from the Darzens annulation undergo facile Meinwald rearrangement,[10] as exemplified by the selective conversion of epoxide **7** to ketone **23** enabled by boron trifluoride etherate at room temperature (Scheme 6).

We next turned our attention to aza-Darzens annulation investigations. It was soon established that sulfinamide imines, which we had employed successfully for dienolates (Scheme 1), were not reactive enough to engage the anions of **1** and **2**, which is why we focused on their oxidized (*tert*-butylsulfonyl = Bus)[11] variants for our studies. After extensive evaluation of a wide array of bases, solvents, temperatures, and addition orders, Cs_2CO_3 in acetonitrile at room temperature was identified as a set of mild reaction conditions that enabled **2** to engage Bus-protected imines (Table 1). Annulations afforded two products in varying ratios depending on the imine, which were confirmed to be a *cis*-aziridine and an enamide.[12] Electron-poor imines favored the formation of *cis*-aziridines (entries 8 and 13 in particular as well as 4, 5, and 12), while electron-rich imines preferentially afforded enamides (entry 10 most notably). The stereochemistry of the aziridine (*cis*) suggests a *syn* addition in the initial Mannich addition step followed by cyclization or, alternatively, a competing 1,2-shift resulting in the enamide product. These electronic trends and observations, consistent with others such as those from the efforts of Templeton[13] and Wulff,[14] are postulated to result from the ability of electron-rich imines to accelerate the hydride (or R) shift after the Mannich addition.

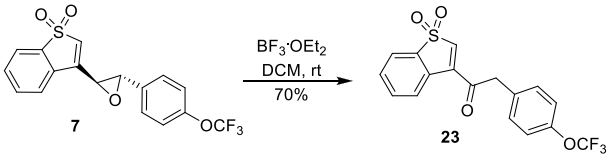
Scheme 4. Scope and Limitations of Darzens Annulation



Scheme 5. *Anti* Addition to Aldehydes Is Favored



Scheme 6. Selective Meinwald Rearrangement



Surprised by the high degree of enamide formation for Bus-protected imines, we decided to investigate other sulfonamide

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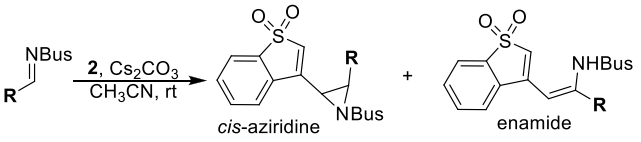
Table 1. Bus-Imine Annulation Studies

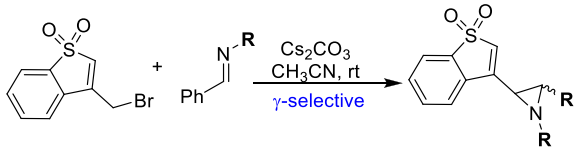


entry	R	aziridine/enamide ratio[a]	*cis*-aziridine yield (%)
1	Ph	1:3	N/A[b]
2	4-NO_2-Ph	1:1.4	N/A
3	4-Br-Ph (**25**)	1:1.1	40
4	4-CN-Ph (**26**)	1.7:1	50
5	4-CF_3-Ph (**27**)	1.4:1	40
6	4-OCF_3-Ph	1:1.8	N/A
7	3-NO_2-Ph	1:1	N/A
8	2-NO_2-Ph (**24**)	4:1	70
9	2-CN-Ph (**31**)	1:1	45
10	2-OMe-Ph	0:1	N/A
11	2-Cl-Ph (**30**)	1:1.4	35
12	3,5-bis-CF_3-Ph (**29**)	2.2:1	50
13	2,4-bis-NO_2-Ph (**28**)	4.6:1	30
14	Ph−CH=CH	NR[c]	NR

[a]Determined by ^{1}H NMR analysis of the crude reaction mixures. [b]N/A indicates that the aziridine and enamide were inseparable. [c]NR indicates that no reaction occurred.

groups to establish whether the Bus group was representative or an outlier. Employing the same reaction conditions, we explored the annulation behaviors of imines protected with mesylate (Ms), besylate (Bes), nosylate (Ns), brosylate (Bs), ansylate (Ans), and tosylate (Ts) groups (Table 2).

Table 2. Aza-Darzens Annulation Protecting-Group Survey



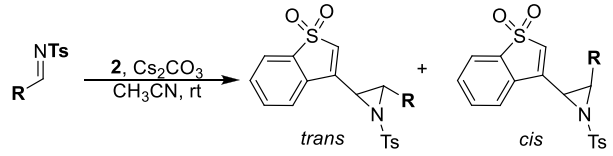
entry	R[a]	yield (%)[b]	*trans*:*cis*[c]
1	Bes	62	3:1
2	Ts	65	3:1
3	Ns	40	2:1
4	Bs	50	3:1
5	Ms	65	2.6:1
6	Ans	54	3:1
7	Boc	0	imine hydrolyzed
8	Dpp	0	imine hydrolyzed

[a]Abbreviations: Bes = besylate; Ts = tosylate; Bs = brosylate; Ms = mesylate; Ans = 4-OMe-$C_6H_4SO_2$-; Boc = *tert*-butoxycarbonyl; Dpp = diphenylphosphinyl. [b]Inseparable mixtures of *trans*- and *cis*-aziridines were isolated. [c]Determined by ^{1}H NMR analysis of the crude reaction mixures.

Interestingly, and in stark contrast to the Bus-protected imines, these six sulfonamide imines did not form enamide products but instead only aza-Darzens aziridine products (Table 2, entries 1−6). The yields were quite similar for these imines, with tosyl performing best. The preferential formation of *trans*-aziridines was an additional departure from what was observed for Bus-protected imines. Perhaps unsurprisingly, Boc and Dpp-protected imines returned hydrolyzed starting material in lieu of aziridines. Appel and Mayr previously quantified the electrophilicity values of various imines in aziridinations, and Bus- and Dpp-protected imines were observed to be far less reactive in comparison to Ts-protected imines.[15] The difference in outcomes for Bus-imines compared with other sulfonamide imides is striking, with steric differences being the most likely explanation, as the *tert*-butyl group of Bus imparts its large size most significantly in the initial *syn* and *anti* Mannich adducts.[16] We postulate that the reason for absence of *trans*-aziridine products in the Bus-imine series is that its precursor Mannich adduct is primarily funneled to a 1,2-shift reaction pathway to form the enamide product instead of the 3-*exo*-*tet* cyclization to produce the *trans*-aziridine.

We decided to explore additional substrates for a representative sulfonamide group, namely, tosylate (Table 3,

Table 3. Aza-Darzens Annulation Scope for Tosylate Imines



entry	R	*trans*:*cis*[a]	yield (%)
1	Ph (**32**)	3:1	65[b]
2	1-Naphth (**33**)	1.8:1	65[b]
3	2-NO_2-Ph (**36**)	1:1.2	40[c]
4	4-OMe-Ph	NA[d]	NR
5	4-OCF_3-Ph (**37**)	2.5:1	47[b]
6	4-Br-Ph (**34**)	3:1	55[b]
7	4-CF_3-Ph (**35**)	2.4:1	50[b]
8	PhCH=CH (**38**)	1:0	40[b]

[a]Determined by ^{1}H NMR analysis of the crude reaction mixures. [b]An inseparable mixture of *trans*- and *cis*-aziridines was isolated. [c]Only the major isomer was isolated and characterized. [d]No aziridine formed, and the starting materials were recovered.

entries 1−8). These studies revealed that electron-rich imines such as 4-methoxyphenyl (entry 4) fail to form any aziridine products, with only starting materials recovered. However, when the methyl group is replaced with a trifluoromethyl group (entry 5), the reaction proceeds to form the expected aziridines, favoring the *trans*-aziridine. With respect to size and electronic factors that impact *cis*/*trans*-aziridine ratios, we have learned that a larger group (entry 2) will diminish the *trans* selectivity slightly, with an *o*-nitro aryl group (entry 3) representing the only case in which the *cis*-aziridine is formed in marginal excess and cinnamyl imines (entry 8) affording the *trans*-aziridine as the only products.

These intriguing imine-dependent aza-Darzens annulation results prompted us also to evaluate acyclic sulfone nucleophile **1**, which had performed poorly in comparison with **2** in converting aldehydes to epoxides. We decided to investigate select Bus- and Ts-protected imines as representatives of the divergence of outcomes presented in Tables 1 and 2. The results of employing **1** under the same reaction conditions are detailed in Scheme 7. Most notably, the Bus-protected imines produced only aziridine products, and no undesired enamides were observed with annulations using cyclic nucleophile **2**. For a phenyl substituent, Bus- and Ts-protected imines (**39** and **40**) behaved identically, while for anisaldehyde-derived imines

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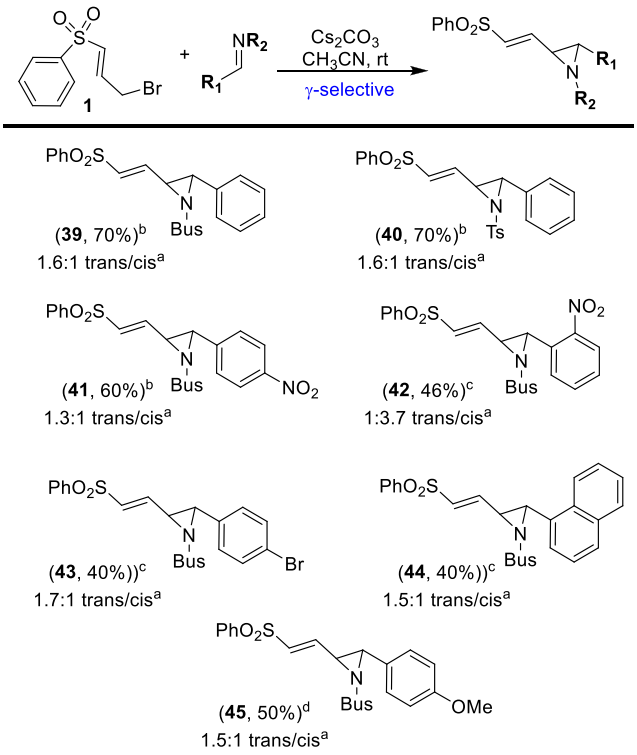
Scheme 7. Acyclic Nucleophile Aza-Darzens Annulations[a]



[a]Determined by ^{1}H NMR analysis of the crude reaction mixure. [b]The two isomers were separable. [c]Only the major isomer was isolated and characterized. [d]An inseparable mixture of *trans*- and *cis*-aziridines was isolated.

the Ts- imine did not react while the Bus-imine did (**45**). Otherwise, the resulting Bus-protected imines (**41**–**44**) followed trends similar to those observed in Table 3, as exemplified, for example, by the fact that the highest *cis*-aziridine ratio was obtained with 2-nitrophenyl imine (**42**). For this series, we also argue that sterics are the main reason why protected Bus-imines shine when reacted with **1** while they struggle in the presence of **2**. The conformational flexibility of **1** exerts far less steric hindrance in the resulting Mannich adducts, thus providing a clear path for 3-*exo*-*tet* cyclization and aziridine formation

In conclusion, we have demonstrated the significant influence of strategic β-substitutions of bromosulfone nucleophiles on the outcomes of vinylogous Darzens and aza-Darzens reactions. Both the optimized epoxidation and aziridination protocols proceed under thermodynamic control under relatively mild reaction conditions. With regard to reaction trends electron-neutral aldehydes performed the best in our epoxidation studies (Darzens reaction), whereas electron-deficient imines where shown afford the highest yields in our aziridination studies (aza-Darzens reaction). The choice of the imine protecting group was demonstrated to be critically important. In this regard, the sterically demanding Bus group was an outlier compared with its sulfonamide counterparts, diverting a significant amount of the Mannich intermediate to an enamide product instead of the aziridine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02448.

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

Accession Codes

CCDC 2000082 contains 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ilardi, E. A.; Njardarson, J. T. Ring Expansions of Vinyloxiranes, -Thiiranes and -Aziridines: Synthetic Approaches, Challenges and Catalytic Success Stories. *J. Org. Chem.* **2013**, *78*, 9533−9540.

(2) Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ($(CH_3)_2SOCH_2$) and Dimethylsulfonium Methylide ($(CH_3)_2SCH_2$). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(3) Newman, M. S.; Magerlein, B. J. The Darzens Glycidic Ester Condensation. *Org. React.* **1949**, *5*, 413−440.

(4) Brichacek, M.; Navarro Villalobos, M.; Plichta, A.; Njardarson, J. T. Stereospecific Ring Expansion of Chiral Vinyl Aziridines. *Org. Lett.* **2011**, *13*, 1110−1113.

(5) Chogii, I.; Njardarson, J. T. Asymmetric [3 + 2] Annulation Approach to 3-Pyrrolines: Concise Total Syntheses of (−)-Supinidine, (−)-Isoretronecanol, and (+)-Elacomine. *Angew. Chem., Int. Ed.* **2015**, *54*, 13706−13710.

(6) Chogii, I.; Das, P.; Delost, M. D.; Crawford, M. N.; Njardarson, J. T. Asymmetric Vinylogous Aza-Darzens Approach to Vinyl Aziridines. *Org. Lett.* **2018**, *20*, 4942−4945.

(7) Gallagher, E. T.; Grayson, D. H. Reactions of Lithiated (*E*)-3-Halo-1-phenylsulfonylprop-1-enes and (*Z*)-1-Halo-3-phenylsulfonylprop-1-enes with Aldehydes. *Org. Biomol. Chem.* **2003**, *1*, 1374−1381.

(8) Bordwell, F. G.; Sokol, P. E.; Spainhour, J. D. Effect of the Leaving group on the Rates of SN2 and SN2' Reactions in Allylic Systems. *J. Am. Chem. Soc.* **1960**, *82*, 2881−2888.

(9) The displacement ellipsoids for **7** are at the 50% probability level.
(10) Meinwald, J.; Labana, S. S.; Chadha, M. S. Peracid Reactions. III. The Oxidation of Bicyclo[2.2.1] Heptadiene. *J. Am. Chem. Soc.* **1963**, *85*, 582−585.
(11) (a) Sun, P.; Weinreb, S. M.; Shang, M. *tert*-Butylsulfonyl (Bus), a New Protecting Group for Amines. *J. Org. Chem.* **1997**, *62*, 8604−8608. (b) García Ruano, J. L.; Alemán, J.; Belén Cid, M.; Parra, A. A General Method for the Preparation of *N*-Sulfonyl Aldimines and Ketimines. *Org. Lett.* **2005**, *7*, 179−182.
(12) Enamide formation has been observed in aza-Darzens aziridination, although in the closest example the exact opposite imine electronic trends were observed. See: Aichhorn, S.; Gururaja, G. N.; Reisinger, M.; Waser, M. Scope and Limitations of Diastereoselective Aziridination Reactions Using Stabilized Ammonium Ylides or α-Bromo Carbonyl Nucleophiles. *RSC Adv.* **2013**, *3*, 4552−4557.
(13) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. Lewis Acid-Catalyzed Synthesis of Aziridines. *J. Org. Chem.* **1996**, *61*, 8358−8359.
(14) (a) Antilla, J. C.; Wulff, W. D. Catalytic Asymmetric Aziridination with a Chiral VAPOL-Boron Lewis Acid. *J. Am. Chem. Soc.* **1999**, *121*, 5099−5100. (b) Antilla, J. C.; Wulff, W. D. Catalytic Asymmetric Aziridination with Arylborate Catalysts Derived from VAPOL and VANOL Ligands. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518−4521.
(15) Appel, R.; Mayr, H. Quantification of the Electrophilic Reactivities of Aldehydes, Imines, and Enones. *J. Am. Chem. Soc.* **2011**, *133*, 8240−8251.
(16) For recent examples of the effect of nitrogen protecting groups on additions of α-halo nucleophiles, consult: (a) Monticelli, S.; Colella, M.; Pillari, V.; Tota, A.; Langer, T.; Holzer, W.; Degennaro, L.; Luisi, R.; Pace, V. Modular and Chemoselective Strategy for the Direct Access to α-Fluoroepoxides and Aziridines via the Addition of Fluoroiodomethyllithium to Carbonyl-Like Compounds. *Org. Lett.* **2019**, *21*, 584−588. (b) Ielo, L.; Touqeer, S.; Roller, A.; Langer, T.; Holzer, W.; Pace, V. Telescoped, Divergent, Chemoselective C1 and C1-C1 Homologation of Imine Surrogates; Access to Quaternary Chloro- and Halomethyl-Trifluoromethyl Aziridines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2479−2484.

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