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Stereospecific Functionalization of Iodoaziridines via Unstabilized Aziridinyllithiums Generated by Iodine−Lithium Exchange

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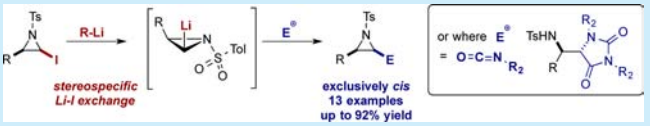
Supporting Information

ABSTRACT: Lithium−iodine exchange on alkyl- or aryl-substituted *N*-tosyliodoaziridines afforded unstabilized aziridinyllithiums, which were subsequently trapped at low temperatures with a range of carbon and heteroatom electrophiles affording *cis*-substituted aziridines exclusively. When using isocyanates as electrophiles, access to aziridine carboxamides or 1,3,5-trisubstituted hydantoins can be selected by control of reaction temperature.



Aziridines are an important class of saturated heterocycles often used as synthetic intermediates.[1,2] The strained three-membered ring is prone to ring-opening with a variety of nucleophiles affording functionalized amines and other valuable *N*-containing compounds.[3,4] Consequently, there is continued interest in developing improved methods for the synthesis of aziridine derivatives.[5] In recent years, there has been significant interest in the divergent synthesis of aziridine derivatives by functionalization of preformed, intact aziridine rings. This has been achieved through the generation of aziridinyl anions and reaction with electrophiles.[6] Unstabilized aziridinyl metal species have been generated by functional-group exchange (SOR,[7] $SnBu_3$,[8] SiR_3[9]) and by direct deprotonation of aziridine derivatives.[10−12] Palladium-catalyzed cross-coupling of metalated aziridine species has also been reported recently by our group[13] and Vedejs[14] to afford aryl- and vinylaziridines.

To date, the generation of *N*-sulfonylaziridinyllithium species has only been possible through deprotonation, though the success of the reaction with electrophiles, as well as the regiochemical outcome, has been dependent on the nature of the *N*-group and the inherent substitution of the aziridine.[6] Notably, external electrophilic trapping of lithiated *N*-tosylaziridines has not been successful,[11] in part due to rapid intramolecular nucleophilic attack at the toluene sulfonyl group (Figure 1A).[15,9] Schaumann and Aggarwal observed that lithiation of phenyl *N*-tosylaziridine derivatives resulted in dearomatization by reaction of the added electrophiles adjacent to the sulfonyl group, yielding a tricyclic product.[15,9] More recently, *N*-Bus (*tert*-butyl sulfonyl) aziridines have been successfully applied in lithiation/trapping sequences (Figure 1B).[11] Hodgson reported that monoalkyl *N*-Bus aziridines undergo regio- and stereoselective deprotonation with LiTMP and that trapping with reactive electrophiles gave *trans*-substituted aziridines.[11a,b] On the other hand, Florio and coworkers observed that aryl substitution on the aziridine ring results in benzylic deprotonation.[11c] It is notable that the anions of these activated aziridines are carbenoid-like[16] and require low temperatures for structural stability. A stabilizing interaction between the sulfonyl group and the lithium has been proposed in these instances to account for stereoselectivity and configurational stability.[11]

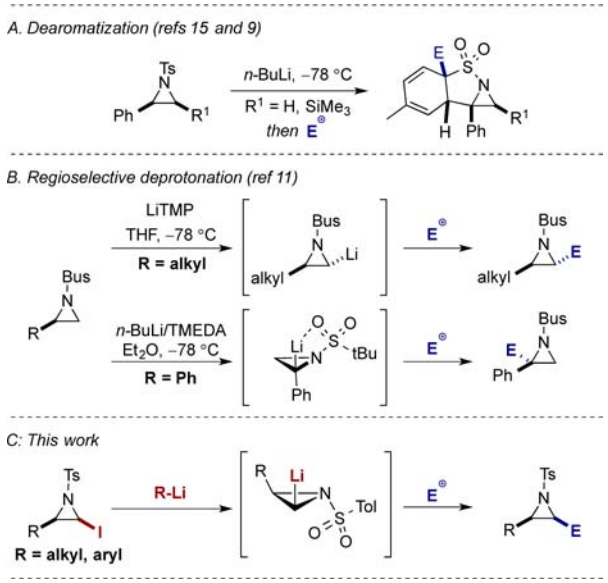


Figure 1. Functionalization of *N*-sulfonylaziridines via aziridinyllithium intermediates keeping the aziridine intact.

We recently reported strategies for the synthesis of a range of aryl-[17] and branched alkyl-substituted *cis*-iodoaziridines.[17b] We envisaged that iodoaziridines could provide suitable precursors for further derivatization of the intact aziridine. In particular, the regio- and stereospecific lithiation by Li−I exchange from *N*-tosyliodoaziridines would afford *cis*-*N*-tosylaziridines (Figure 1C) and provide complementary stereo- and regiochemical access to *N*-sulfonylaziridinyllithium species versus deprotonation approaches. The success of this strategy would be reliant upon several factors: (i) the lithiated aziridine must be

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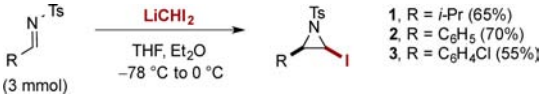
sufficiently structurally stable to avoid degradation or other possible reactions (e.g., carbenoid dimerization, ring-opening);[12] (ii) the lithiated aziridine must be formed and react stereospecifically with retention, and be configurationally stable to afford the *cis* product; (iii) the *N*-tosyl group must remain *trans* to C−Li to avoid addition to the tosyl group;[15] this is likely the preferred conformation due to the presence of the R-group, but precludes the possibility of stabilizing interactions by coordination of the sulfonyl oxygen with lithium; and (iv) to ensure regiospecific reaction with aryl-substituted aziridines, the anion must not equilibrate to the more stabilized benzylic position.

Here, we report the successful stereospecific lithiation of *N*-tosyliodoaziridines and trapping with a range of electrophiles to afford *cis*-substituted aziridines in high yields with alkyl- and aryl-substituted iodoaziridine derivatives. We also report the selective synthesis of a range of 1,3,5-substituted hydantoins using aryl and alkyl isocyanates via a lithium−iodine exchange, trapping, and aziridine ring-opening sequence.

Lithium−halogen exchange is a highly effective and rapid process for the generation of organolithium species from the corresponding halides, driven by pK_a considerations.[18] Knochel recently reported the generation of stereodefined acyclic organolithium compounds and also axial and equatorial cyclohexyllithium derivatives from iodides using *t*-BuLi.[19] High retention of the stereochemical configuration at the reacting center was achieved on trapping with reactive electrophiles. We started our studies from iodoaziridine **1** (Scheme 1), intending to submit to conditions for lithium−

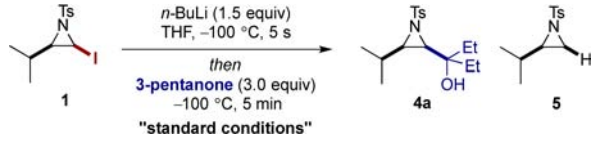
Scheme 1. Preparation of Iodoaziridine Substrates



iodine exchange and then trap with electrophiles. *cis*-Iodoaziridines **1**−**3** were prepared in gram quantities according to our previously reported method by the addition of diiodomethyllithium to *N*-tosylimines and highly stereoselective cyclization.[20]

Our initial studies used *t*-BuLi, with temperature control found to be crucial. Performing the reaction at −100 °C rapidly generated the aziridinyllithium, which could be trapped keeping the ring intact. However, from the perspective of cost and safety, we chose to further develop the reaction using *n*-BuLi. The exchange was also rapid with this reagent, and there was no apparent reaction of the lithiated intermediate with the generated *n*-BuI at the low reaction temperature. After extensive experimentation we established a robust and reproducible protocol to generate the desired aziridinyllithium and react with 3-pentanone in high yields (Table 1, entry 1). The procedure involved the addition of a solution of the aziridine in THF to a solution of 1.5 equiv of *n*-BuLi at −100 °C. After 5 s, the lithiation was complete and an excess of electrophile was added to afford an 83% yield of desired aziridine **4a** (measured by ^{1}H NMR spectroscopy against an internal standard), along with a small amount of protonated aziridine **5**. Each parameter was varied during optimization, and selected results are included in Table 1. Reduced quantities of *n*-BuLi (1.2 equiv) led to recovered starting iodide, which was improved using a longer time for the lithiation step **4a** (Table 1, entries 2 and 3).

Table 1. Optimization of Li−I Exchange Protocol and Trapping of Aziridinyllithium with 3-Pentanone



		yield[b] (%)		
entry	deviation from standard conditions[a]	**4a**	**5**	**1**[c]
1	none	83	17	0
2	*n*-BuLi (1.2 equiv)	61	22	14
3	*n*-BuLi 91.2 equiv)/30 s lithiation	76	15	0
4	reaction run at −78 °C	11	36	4
5	hexane/Et_2O (3:2), instead of THF	10	23	54
6	hexane/THF (3:2), instead of THF	46	29	17
7	THF/Et_2O (3:2), instead of THF	73	17	0
8	no 3-pentanone	0	90 (86)[d]	0
9	concentration = 0.065 M[e]	84 (81)[d]	11	0

[a]Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.13 M), −100 °C; then addition of aziridine (0.27 mmol) in THF, 5 s; then 3-pentanone (3.0 equiv), THF, −100 °C, 5 min. [b]Yield determined by ^{1}H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). [c]Unreacted iodoaziridine **1**. [d]Isolated yield. [e]*n*-BuLi concentration before aziridine addition.

Performing the reaction at −78 °C gave poor results due to the structural instability of the unstabilized anion at this increased temperature. Toluene sulfonamide was the major identifiable product at this temperature.[16b] Various solvent combinations were attempted, aiming to reduce the formation of aziridine **5** (Table 1, entries 5−7), including those successfully used by Knochel.[19] With iodoaziridine **1**, THF alone was found to be superior to being in combination with *n*-hexane or diethyl ether, which may be due in some part to poor solubility of the iodoaziridine in these systems. In the absence of the addition of 3-pentanone under the optimized reaction conditions, protonated aziridine **5** was formed in high yield after the 5 min reaction time (Table 1, entry 8). No significant degradation of the lithiated aziridine was observed in this time frame, indicating structural stability at low temperature, and addition to the *N*-tosyl group was also not observed, which suggests configurational stability. Ultimately, we chose to perform the reaction under the more dilute conditions to investigate the reaction scope (Table 1, entry 9), to aid temperature control during addition of the aziridine and electrophile.

The scope of the reaction was explored varying the electrophile (Scheme 2), forming exclusively *cis*-substituted aziridines in all cases. Under the final conditions, a yield of 81% was obtained for **4a**. Alkyl and aromatic aldehydes both provided the corresponding *cis*-aziridinyl alcohols **4b** and **4c**, respectively, in excellent yield.[21] Reaction with 5 equiv of MeOD afforded deuterated aziridine **4d** with 95%-D incorporation.

cis-Heteroatom-substituted aziridines, silane **4e** and sulfide **4f**, were accessed via trapping of the aziridinyllithium species with Me_3SiCl and $(PhS)_2$ respectively. In the case of $(PhS)_2$, butyl phenyl sulfide was observed in the crude mixture due to the reaction of *n*-BuI generated in the I/Li exchange with the phenyl thiolate leaving group. This may act to protect the aziridine product from ring-opening with the thiolate nucleophile. *cis*-Aziridine aldehyde **4g** was accessed by trapping

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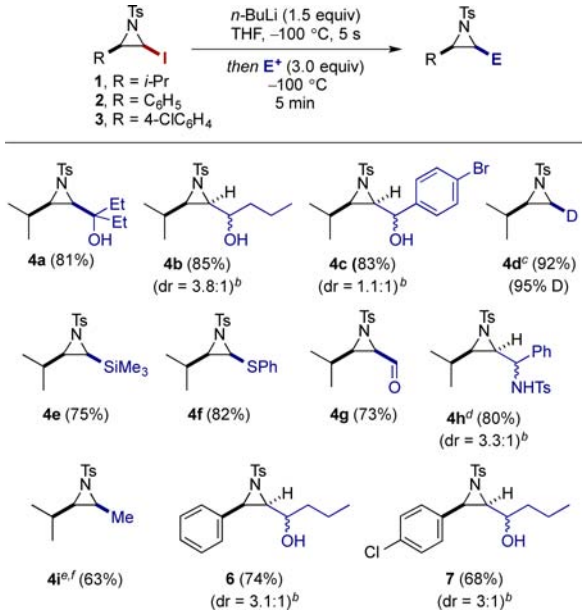
Scheme 2. Formation of *cis*-Substituted Aziridines via Li−I Exchange/Electrophilic Trapping[a]



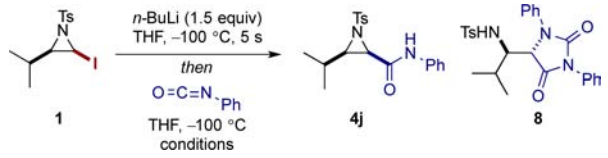
[a]Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M) −100 °C, addition of aziridine (0.27 mmol) in THF, 5 s; then electrophile (3.0 equiv), THF, −100 °C, 5 min. dr observed by ^{1}H NMR spectroscopy in crude reaction mixture. 5.0 equiv of MeOD used. 1.0 equiv of imine used. Reaction mixture warmed to −90 °C. Contained **5** as an inseparable impurity (13% yield). Yield for **4i** calculated on the basis of desired product only.

the aziridinyllithium with DMF. Reaction with 1 equiv of phenyl *N*-tosyl imine gave rise to a mixture of *cis*-aziridine amines in excellent yield and modest dr at the newly formed stereocenter. No reaction occurred between the aziridinyllithium and iodomethane under the optimized conditions. However, methylation could be promoted by warming the reaction mixture to −90 °C to afford the *cis*-aziridine **4i**. Aryl-substituted aziridines **2** and **3** were subjected to the optimized conditions and trapping with butyraldehyde, and *cis*-aziridines **6** and **7** were formed exclusively, with no reaction at the benzylic position. In all cases, only the *cis*-substituted aziridine was observed, supported by coupling constants in the ^{1}H NMR spectrum of the crude reaction mixture (e.g., for aziridine **4a**, δ 2.88 ppm, J = 7.2 Hz for the aziridine C*H*(CEt_2OH); cf. J = 4−5 Hz for typical *trans*-aziridine substitution).[11] This stereochemical outcome suggests that the Li−I exchange occurs without the involvement of radical intermediates, which would be expected to afford epimerization.[18]

Initial attempts to trap the lithiated intermediate with phenyl isocyanate showed interesting further reactivity after the initial electrophilic trapping. The anticipated product **4j** was formed along with cyclized hydantoin **8** as a single diastereoisomer (Table 2, entry 1).

Hydantoins are interesting scaffolds in medicinal chemistry and are found in many biologically active compounds.[22] As this approach afforded a rapid synthesis of substituted hydantoins as single diastereoisomers, we optimized for the formation of this product. Prolonged reaction time gave rise to increased amounts of hydantoin **8** (Table 2, entry 2). Warming of the reaction mixture after the addition of phenyl isocyanate led further increases in the formation of the hydantoin (Table 2,

Table 2. Formation of 1,3,5-Trisubstituted Hydantoin via Intramolecular Aziridine Ring-Opening



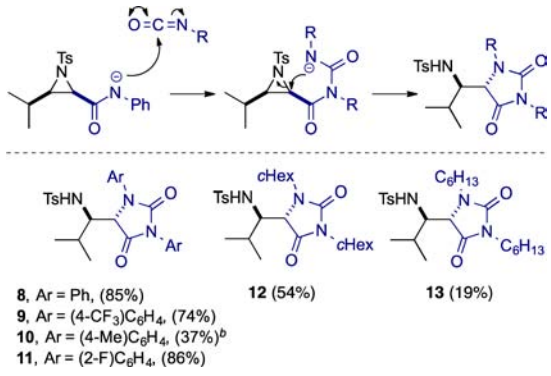
entry	conditions	4j/8[a]	yield (%)
1	−100 °C, 5 min	6.8:1	**4j**, 65
2	−100 °C, 10 min	2.4:1	
3	warm to −90 °C, 5 min	3.8:1	
4	warm to −78 °C, 5 min	1.5:1	
5	warm to −0 °C, 5 min	**8** only	**8**, 85

[a]Ratio from ^{1}H NMR spectroscopy of crude reaction mixture.

entries 3 and 4). Full conversion to hydantoin **8** was achieved by warming the reaction mixture to 0 °C directly after addition of the electrophile, leading to the formation of hydantoin **8** as a single diastereoisomer in 85% yield.

Mechanistically, we propose that the amide anion generated by the first addition reacts with the excess phenyl isocyanate (Scheme 3).[23] From this compound, aziridine opening (5-exo-

Scheme 3. Proposed Mechanism and Examples of Formation of Hydantoins Using Isocyanates as Electrophiles[a]



[a]Reaction conditions: *n*-BuLi (1.5 equiv), THF (0.065 M) −100 °C, addition of aziridine (0.27 mmol) in THF, 5 s; then isocyanate (3.0 equiv), THF, −100 °C, then 0 °C, 5 min. Aziridine carboxamide **4k** also isolated in 44% yield.

tet) afforded the hydantoin as a single diastereoisomer. A range of isocyanates were then examined under conditions to the form the 1,3,5-trisubstituted hydantoins from iodoaziridine **1**. Aryl isocyanates afforded hydantoins **8**−**11**. Monoaddition was also observed with the more electron-rich isocyanate to afford **4k** alongside **10**, indicating a slower second addition. Primary and secondary alkyl isocyanates were also employed to access *N*-alkyl 1,3,5-trisubstituted hydantoins (**12** and **13**).

In summary, we have established an effective lithium−iodine exchange protocol from alkyl and aryl iodoaziridines, leading to their stereospecific functionalization with a broad range of electrophiles in high yields. *cis*-substituted aziridines are formed exclusively, providing a complementary stereochemical outcome compared to methods involving the deprotonation of *N*-sulfonylaziridines. The Li−I exchange occurs rapidly even at low temperature, allowing the unstabilized organolithium to be generated and trapped cleanly without decomposition or side reaction. In addition, a route has been developed to interesting

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1,3,5-trisubstituted hydantoins as single diastereoisomers, using isocyanates as electrophiles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (b) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.

(2) For reactivity of *C*-heteroatom substituted aziridines, see: Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080.

(3) (a) Nielsen, D. K.; Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 13605. (b) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541. (c) Duda, M. L.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 18347. (d) Lu, P. *Tetrahedron* **2010**, *66*, 2549. (e) Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662.

(4) For ring expansion and rearrangements, see: (a) Ilardi, E. A.; Njardarson, J. T. *J. Org. Chem.* **2013**, *78*, 9533. (b) Dauban, P.; Malik, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 9026.

(5) For *N*-transfer to alkenes, see: (a) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. *Science* **2014**, *343*, 61. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. For aza-Darzens reactions, see: (c) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911. (d) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892. For organocatalytic approaches, see: (e) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703. (f) Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5538. (g) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem.—Eur. J.* **2011**, *17*, 7904.

(6) (a) Florio, S.; Luisi, R. *Chem. Rev.* **2010**, *110*, 5128. (b) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. (c) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. P. *Pure Appl. Chem.* **2007**, *79*, 269.

(7) (a) Satoh, T.; Fukuda, Y. *Tetrahedron* **2003**, *59*, 9803. (b) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891. (c) Satoh, T.; Ozawa, M.; Takano, K.; Chyouma, T.; Okawa, A. *Tetrahedron* **2000**, *56*, 4415. (d) Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973.

(8) (a) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607. (b) Vedejs, E.; Little, J. *J. Am. Chem. Soc.* **2002**, *124*, 748. (c) Vedejs, E.; Little, J. D.; Seaney, L. M. *J. Org. Chem.* **2004**, *69*, 1788. (d) Wiedner, S. D.; Vedejs, E. *Org. Lett.* **2010**, *12*, 4030.

(9) (a) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335. (b) Aggarwal, V. K.; Ferrara, M. *Org. Lett.* **2000**, *2*, 4107.

(10) (a) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276. (b) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941. (c) Vedejs, E.; Bhanu Prasad, A. S.; Kendall, J. T.; Russel, J. S. *Tetrahedron* **2003**, *59*, 9849. (d) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749. (e) Hodgson, D. M.; Humphreys, P. G.; Xu, Z.; Ward, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2245.

(11) (a) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153. (b) Hodgson, D. M.; Hughes, S. P.; Thompson, A. L.; Heightman, T. D. *Org. Lett.* **2008**, *10*, 3453. (c) Musio, B.; Clarkson, G. J.; Shipman, M.; Florio, S.; Luisi, R. *Org. Lett.* **2009**, *11*, 325. (d) For use of 1,3,5-triisopropylphenyl sulfonyl derivatives, see: Huang, J.; Moore, S. P.; O'Brien, P.; Whitwood, A. C.; Gilday, J. *Org. Biomol. Chem.* **2009**, *7*, 335.

(12) For ring-opening reactions of lithiated aziridine derivatives, see: (a) Schmidt, F.; Keller, F.; Vedrenne, E.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1149. (b) Coote, S. C.; Moore, S. P.; O'Brien, P.; Whitwood, A. C.; Gilday, J. *J. Org. Chem.* **2008**, *73*, 7852. (c) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009. (d) Hodgson, D. M.; Miles, S. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 935. (e) Moore, S. P.; Coote, S. C.; O'Brien, P.; Gilday, J. *Org. Lett.* **2006**, *8*, 5145. (f) Rosser, C. M.; Coote, S. C.; Kirby, J. P.; O'Brien, P.; Caine, D. *Org. Lett.* **2004**, *6*, 4817. (g) Hodgson, D. M.; Štefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, *3*, 2234.

(13) Hughes, M.; Boultwood, T.; Zeppetelli, G.; Bull, J. A. *J. Org. Chem.* **2013**, *78*, 844.

(14) (a) Nelson, J. M.; Vedejs, E. *Org. Lett.* **2010**, *12*, 5085. (b) Theddu, N.; Vedejs, E. *J. Org. Chem.* **2013**, *78*, 5061.

(15) Breternitz, H.-J.; Schaumann, E.; Adiwidjaja, G. *Tetrahedron Lett.* **1991**, *32*, 1299.

(16) (a) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2006**, *8*, 995. (b) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779.

(17) (a) Bull, J. A.; Boultwood, T.; Taylor, T. A. *Chem. Commun.* **2012**, *48*, 12246. (b) Boultwood, T.; Affron, D. P.; Trowbridge, A. D.; Bull, J. A. *J. Org. Chem.* **2013**, *78*, 6632. (c) Boultwood, T.; Affron, D. P.; Bull, J. A. *J. Visualized Exp.* **2014**, DOI: 10.3791/51633.

(18) (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, U.K., 2002. (b) Seyferth, D. *Organometallics* **2006**, *25*, 2. (c) Bailey, W.; Patricia, J. *J. Organomet. Chem.* **1988**, *352*, 1. (d) Barl, N. M.; Werner, V.; Sämann, C.; Knochel, P. *Heterocycles* **2014**, *88*, 827.

(19) (a) Kuzmina, O. M.; Steib, A. K.; Markiewicz, J. T.; Flubacher, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 4945. (b) Dagousset, G.; Moriya, K.; Mose, R.; Berionni, G.; Karaghiosoff, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1425.

(20) See ref 17b and the Supporting Information for further details.

(21) For recent examples of oxidation of *N*-sulfonylaziridinyl alcohols to diastereomerically pure aziridinyl ketones, see ref 11b,d and: Moore, S.; O'Brien, P.; Whitwood, A.; Gilday, J. *Synlett* **2008**, 237.

(22) (a) Mehta, N. B.; Diuguid, C. A. R.; Soroko, F. E. *J. Med. Chem.* **1981**, *24*, 465. (b) Marton, J.; Enisz, J.; Hosztafi, S.; Timar, T. *J. Agric. Food Chem.* **1993**, *41*, 148−152. (c) El-Barbary, A. A.; Khodair, A. I.; Pedersen, E. B.; Nielsen, C. *J. Med. Chem.* **1994**, *37*, 73. (d) Comber, R. N.; Reynolds, R. C.; Friedrich, J. D.; Manguikian, R. A.; Buckheit, R. W.; Truss, J. W.; Shannon, W. M.; Secrist, J. A. *J. Med. Chem.* **1992**, *35*, 3567.

(23) Miura, T.; Mikano, Y.; Murakami, M. *Org. Lett.* **2011**, *13*, 3560.