Organic LETTERS

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Generation and Electrophile Trapping of *N*-Boc-2-lithio-2-azetine: Synthesis of 2-Substituted 2-Azetines

David M. Hodgson,* Christopher I. Pearson, and Madiha Kazmi

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information

ABSTRACT: *s*-BuLi-induced α-lithiation−elimination of LiOMe from *N*-Boc-3-methoxyazetidine and further in situ α-lithiation generates *N*-Boc-2-lithio-2-azetine which can be trapped with electrophiles, either directly (carbonyl or heteroatom electrophiles) or after transmetalation to copper (allowing allylations and propargylations), providing a concise access to 2-substituted 2-azetines.

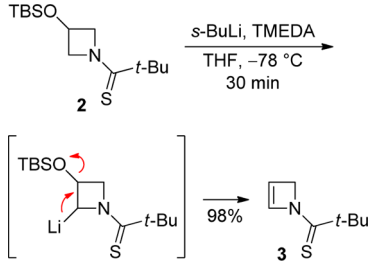
2-Azetidinones (β-lactams) and azetidines are well-studied four-membered azacyclic systems with important biological activities.[1] In contrast, the unsaturated and more strained 2-azetine (1,2-dihydroazete) system **1** (Figure 1) is comparatively less explored, which partly reflects issues of ease of access and stability (notably the propensity to undergo 4e electrocyclic ring-opening to 1-azabutadienes), although electron-withdrawing groups on the nitrogen are known to reduce instability.[2,3]

1

Figure 1. 2-Azetine **1**.

As part of a program with the aim of providing flexible and divergent routes to substituted 4-membered azacycles involving substituent incorporation onto a pre-existing and straightforwardly accessed azetidine core, we recently reported α-lithiation−electrophile trapping of *N*-thiopivaloylazetidine[4] and -azetidin-3-ol[5] in enantio- and diastereocontrolled processes, respectively. During the development of the latter work, we found that the unprotected 3-hydroxyl group was essential, as protection (e.g., as the TBS ether **2**) only led to efficient elimination on attempted α-lithiation−electrophile trapping, to generate the corresponding stable 2-azetine **3** (98%) (Scheme 1).[5] This observation led us to consider the possibility of α-electrophile incorporation using *N*-protected 2-azetine, in which the unsaturation retained in the adducts could provide a site for further synthetic manipulation. Here we communicate our promising preliminary results in this area.

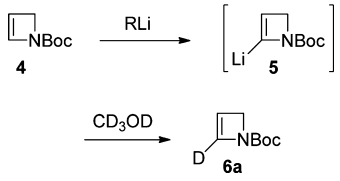
Scheme 1. Lithiation−Elimination of Silyloxythioamide 2[5]



2 **3**

While *N*-protection/activation with the thiopivaloyl group had been found to be uniquely successful in enabling α-lithiation−electrophile trapping of azetidine and 3-hydroxyazetidine,[4,5] with 2-azetine **3** only modest isolated yields of trapped products (~15% using either MeI or BnBr) could be obtained despite extensive experimental investigations.[6] We therefore turned our attention to alternative nitrogen protection. Following pioneering studies by Beak and co-workers, Boc protection now is well-established for facilitating α-lithiation−electrophile trapping of normal-sized azacycles[7] (including Csp^2 α-lithiation of 1,2,3,4-tetrahydropyridine[8]), although simple *N*-Boc aziridines undergo rapid N→C Boc migration following α-lithiation.[9] In the present case, we were pleased to find that the known *N*-Boc-2-azetine (**4**)[10] underwent regioselective lithiation at the α-sp^2 position[11] followed by deuteration to give 2-D-2-azetine **6a** (54% yield, 100% D, Scheme 2) under conditions typically used with *N*-Boc heterocycles [*s*-BuLi (1.2 equiv), TMEDA (1.2 equiv), THF, −78 °C, 1 h]. Further experimentation established that *n*-BuLi was similarly effective (56%); the absence of TMEDA did not affect the yield (54%), and LiTMP (1.4 equiv, THF, −78 °C, 45 min) also delivered sp^2 α-lithiation−trapping (70%).

Scheme 2. Lithiation−Deuteration of *N*-Boc-azetine (4)



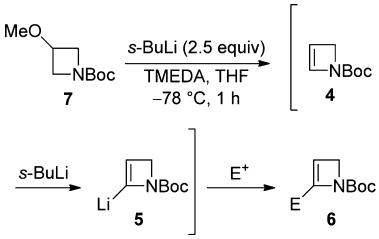
4 **5** **6a**

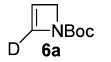
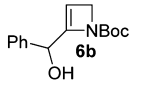
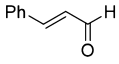
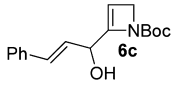
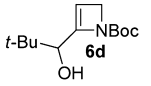
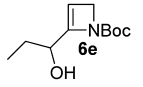
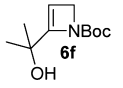
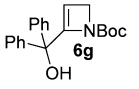
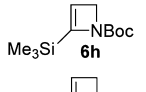
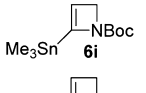
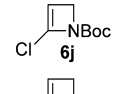
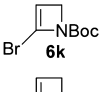
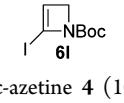
Despite the above encouraging preliminary results, yield variability in duplicate lithiation−deuteration experiments,

Received: December 16, 2013
Published: January 10, 2014

   dx.doi.org/10.1021/ol403626k | *Org. Lett.* 2014, 16, 856−859

Table 1. Scope of Carbonyl and Heteroatom Electrophiles with Li-azetine 5



entry	electrophile	azetine **6**	yield of **6**
1	CD_3OD	 **6a**	88% (100% D)
2		 **6b**	97%
3		 **6c**	78%
4		 **6d**	84%
5		 **6e**	82%
6		 **6f**	44%
7		 **6g**	51%[a]
8	Me_3SiCl	 **6h**	74%
9	Me_3SnCl	 **6i**	76%
10	Cl_3CCCl_3	 **6j**	63%
11	$BrCl_2CCBrCl_2$	 **6k**	71%
12	I_2	 **6l**	60%

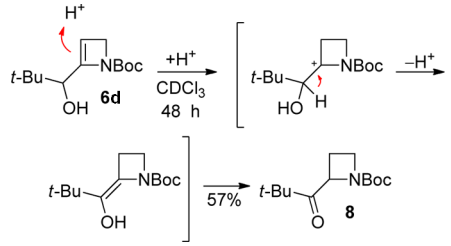
[a]Yield corrected for inseparable *N*-Boc-azetine **4** (10% by ^{1}H NMR analysis).[12]

together with modest yields in the synthesis of *N*-Boc-azetine (**4**) [previously prepared (46%) by *t*-BuOK-induced elimination from the corresponding 3-tosylate;[10] in our hands, elimination (66%) by way of the 3-chloride was preferred[12]] and the instability/tendency of unsubstituted *N*-Boc-azetine (**4**) to polymerize when left at rt and slowly during storage at −20 °C, led us to consider a modified strategy[7b,8] where the unsubstituted *N*-Boc-2-azetine (**4**) was generated and lithiated in situ. This approach resulted in an efficient and reproducible method to 2-D **6a** (88% yield, 100% D) when *N*-Boc-3-methoxyazetidine (**7**), available commercially or readily prepared by methylation (NaH, MeI, quant)[12] of widely available *N*-Boc-azetidin-3-ol, was reacted with 2.5 equiv of *s*-BuLi.[13] The scope of the reaction with respect to electrophile variation was investigated following these conditions (Table 1).

Aldehydes (Table 1, entries 2−5) and ketones (entries 6 and 7), including an enal (entry 3) and potentially enolizable substrates (entries 5 and 6), provided the corresponding secondary and tertiary alcohols **6b−g** in generally good yields. Using carbonyl-based electrophiles at a higher oxidation level (BzCl, ethyl chloroformate, Mander's reagent) or alkylating agents (MeI, BuI, BnBr, allyl bromide) did not prove viable, only resulting in the isolation of *N*-Boc azetine **4** or decomposition of starting materials. However, heteroatom incorporation could be achieved, generating the corresponding silylated (entry 8), stannylated (entry 9), and halogenated 2-azetines (entries 10−12), although in these latter cases reversed-phase chromatography[14] was necessary for satisfactory product isolation.

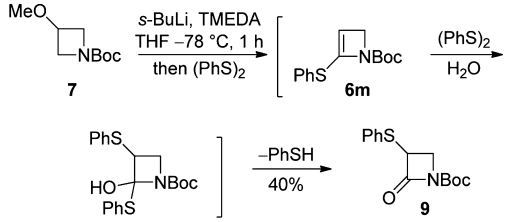
Observations with two electrophiles (pivalaldehyde and diphenyl disulfide) show further reactivity following electrophile trapping. While the hindered alcohol **6d** derived from pivalaldehyde could be isolated in good yield as indicated (84%, Table 1, entry 4), exposure to $CDCl_3$ which had not been passed through alumina prior to use resulted in prototropy[15] driven by relief of strain, to the corresponding saturated ketone **8** (57%, Scheme 3); other aldehyde-derived adducts did not undergo analogous isomerizations.

Scheme 3. Isomerization of Alcohol 6d to Ketone 8



Reaction with diphenyl disulfide (2.5 equiv) led, unusually, to *N*-Boc-α-phenylthio-β-lactam (**9**) (40%, Scheme 4). The

Scheme 4. β-Lactam 9 from 3-Methoxyazetidine 7



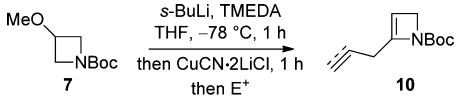
formation of β-lactam **9** may proceed through initial electrophile trapping where the resulting electron-rich azetine **6m** undergoes further reaction with the electrophile, followed by hydrolysis (Scheme 4); reduction in the quantity of $(PhS)_2$ used (to 0.9 or 1.0 equiv) did not result in recovery of any identifiable products.

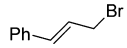
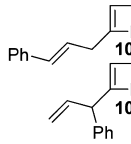
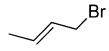
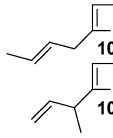
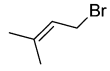
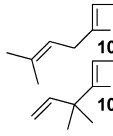
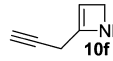
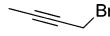
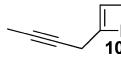
While direct allylation of lithiated azetine **5** had proven problematic, transmetalation to the organocopper[16] allowed C−C bond formation by nucleophilic substitution to give allylated and propargylated azetines **10** (Table 2).

Simple allylation and methallylation proceeded satisfactorily (Table 2, entries 1 and 2). With unsymmetrical allylic bromides

dx.doi.org/10.1021/ol403626k | *Org. Lett.* 2014, 16, 856−859

Table 2. Scope of Copper-Mediated Allylation and Propargylation



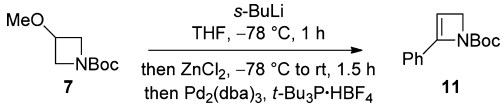
entry	electrophile	azetine **10**	yield of **10**
1		 **10a**	60%
2		 **10b**	55%
3		 **10c** / **10c′**	50% **10c:10c′** 100:0[a]
4		 **10d** / **10d′**	78% **10d:10d′** 47:53[a]
5		 **10e** / **10e′**	64% **10e:10e′** 61:39[a]
6		 **10f**	37%
7		 **10g**	46%

[a]Isolated ratio after chromatography.

(cinnamyl, crotyl, and prenyl), mixtures of S_N2- and S_N2'-derived azetines were observed [S_N2:S_N2' by crude ^{1}H NMR analysis, 91:9 (entry 3), 47:53 (entry 4), 66:33 (entry 5)], while propargylation proceeded by S_N2 (entries 6 and 7). The latter contrasts with S_N2' regioselectivity giving allenes seen with *N*-Boc-α-aminoalkylcuprates.[17]

While attempted Suzuki cross-couplings with bromide **6k** did not prove viable, Negishi coupling[18,19] gave 2-phenylated azetine **11** in 27% yield (Scheme 5).

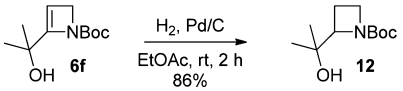
Scheme 5. Phenylated Azetine 11 by Negishi Cross-Coupling



Hydrogenation[3b] of a carbonyl-derived azetinol **6f** provided straightforward access to the corresponding saturated azetidine alcohol **12** (86%, Scheme 6); as noted previously, such adducts are not available by α-lithiation−electrophile trapping of *N*-Boc-azetidine, although *N*-thiopivaloylazetidine is a viable substrate.[4]

In summary, commercially available *N*-Boc-3-methoxyazetidine (**7**) has been shown to undergo α-lithiation−elimination to form *N*-Boc-azetine (**4**) in situ, which can be further α-lithiated regioselectively at the sp^2 center[8,11] and trapped with a range of electrophiles, including allylic and propargylic halides

Scheme 6. Hydrogenation of a 2-Substituted Azetine



by way of transmetalation to copper, providing a direct entry to 2-substituted *N*-Boc azetines. 2-Azetine stability depends significantly on the electron-withdrawing ability of the *N* substituent (aryl, sulfonyl, acyl, alkoxy carbonyl); our work demonstrates that the comparatively modestly electron-withdrawing Boc group is sufficient to allow isolation of 2-substituted 2-azetines, provided they are handled, and in many cases stored, under basic conditions. These studies indicate that electrophile incorporation can be achieved on simple monocyclic azetines and suggest that further opportunities exist for azetine diversity generation using this strategy, with potential to access substituted azetidines through double bond manipulation.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: david.hodgson@chem.ox.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank AstraZeneca and the EPSRC for studentship support (to C.I.P.) and the Higher Education Commission of Pakistan for an IRSIP scholarship (to M.K.).

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(2) (a) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds: Small Ring Heterocycles - Part 2*; Hassner, A., Ed.; Wiley: New York, 1983; Part 2, pp 1−217. (b) Jubault, P.; Leclerc, E.; Quirion, J.-C. In *Science of Synthesis*; Molander, G. A., Ed.; Thieme: Stuttgart, 2006; Vol. 33, pp 577−582.

(3) For recent studies, see: (a) Mangelinckx, S.; Van Speybroeck, V.; Vansteenkiste, P.; Waroquier, M.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 5481−5488. (b) Barluenga, J.; Riesgo, L.; Lonzi, G.; Tomás, M.; López, L. A. *Chem.—Eur. J.* **2012**, *18*, 9221−9224.

(4) Hodgson, D. M.; Kloesges, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2900−2903.

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(6) Chromatographic purification of these substituted thioamide azetines proved challenging, usually resulting in significant loss of material, and with products typically eluting with nonpolar byproducts.

(7) (a) Beak, P.; Lee, W.-L. *Tetrahedron Lett.* **1989**, *30*, 1197−1200. (b) Beak, P.; Lee, W. L. *J. Org. Chem.* **1993**, *58*, 1109−1117. (c) Gawley, R. E.; O'Connor, S.; Klein, R. In *Science of Synthesis*; Snieckus, V., Majewski, M., Eds.; Thieme: Stuttgart, 2006; Vol. *8a*, pp 677−757.

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(9) (a) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749−3752. (b) Hodgson, D. M.; Humphreys, P. G.; Xu, Z.; Ward, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2245−2248. (c) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009−10021.
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(12) See the Supporting Information for details.
(13) *s*-BuLi without TMEDA gave 2-D-2-azetine **6a** (74% 100% D). LiTMP (2.5 equiv, THF −78 °C) gave 2-D-2-azetine **6a** (62%, 100% D) after 5 h (48%, 100% D after 30 min).
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(19) No 2-phenylated azetine **11** was isolated if TMEDA was present; see also ref 18c.

■ NOTE ADDED AFTER ASAP PUBLICATION

Title and numbering in Scheme 3 were incorrect in the version published ASAP on January 10, 2014; the correct version reposted on January 13, 2014.