JOC The Journal of Organic Chemistry

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α- and α′-Lithiation−Electrophile Trapping of *N*-Thiopivaloyl and *N*-*tert*-Butoxythiocarbonyl α-Substituted Azetidines: Rationalization of the Regiodivergence Using NMR and Computation

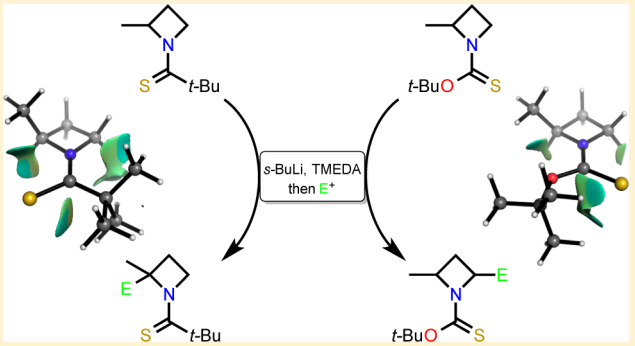
Kelvin E. Jackson,[†] Claire L. Mortimer,[†] Barbara Odell,[†] Jeffrey M. McKenna,[‡,§] Timothy D. W. Claridge,*[,†] Robert S. Paton,*[,†] and David M. Hodgson*[,†]

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

[‡]Novartis Institutes for BioMedical Research, Wimblehurst Road, Horsham, West Sussex RH12 5AB, U.K.

Supporting Information

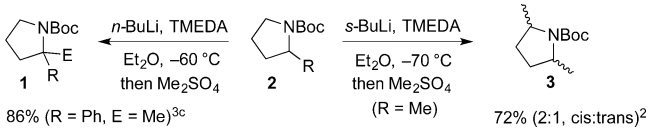
ABSTRACT: ^{1}H NMR and computational analyses provide insight into the regiodivergent (α- and α′-) lithiation−electrophile trapping of *N*-thiopivaloyl- and *N*-(*tert*-butoxythiocarbonyl)-α-alkylazetidines. The magnitudes of the rotation barriers in these azetidines indicate that rotamer interconversions do not occur at the temperature and on the time scale of the lithiations. The NMR and computational studies support the origin of regioselectivity as being thiocarbonyl-directed lithiation from the lowest energy amide-like rotameric forms (*cis* for *N*-thiopivaloyl and *trans* for *N*-*tert*-butoxythiocarbonyl).



INTRODUCTION

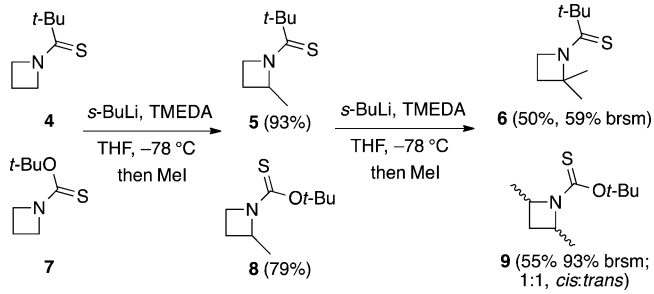
Reaction of an α-C−H bond of a suitably *N*-protected/activated amine is a fundamentally important strategy for the convergent assembly of α-branched amines, with a number of methods applicable to saturated azacycles.[1] α-Lithiation−electrophilic substitution for the latter systems when they are unsymmetrical typically occurs at the less-hindered and/or more acidic site (e.g., from 2-substituted pyrrolidines **2**, Scheme 1),[2−4] provided the *N*-protecting/activating group (often Boc) can coordinatively direct the base to that position under the reaction conditions.[5,6]

Scheme 1. Lithiation−Electrophile Trapping of α-Substituted *N*-Boc-pyrrolidines 2



Azetidines are found in drug leads and bioactive natural products and also find utility as ligands in metal-catalyzed transformations.[7] We recently reported a way to make substituted azetidines by lithiation−electrophile trapping at an α-methylene group, for which only the *N*-thiopivaloyl[8] and *N*-*tert*-butoxythiocarbonyl (*N*-Botc)[9] groups were effective (e.g., **4** → **5** and **7** → **8**, respectively, Scheme 2). In preliminary studies to extend the chemistry to generate more substituted systems, we found that the thiopivaloyl group unusually directs lithiation to an already substituted and unactivated 2-position (**5** → **6**, Scheme 2), whereas the *N*-Botc group led to a 2,4-disubstituted system (**8** → **9**, Scheme 2).[9] Herein, we provide more details on this study, including a comprehensive ^{1}H NMR and computational analysis of these systems, which provide insight into and rationalization of the origin of the regiodivergent observations.

Scheme 2. Lithiation−Methylation of *N*-Thiopivaloyl- and *N*-(*tert*-Butoxythiocarbonyl)azetidines[8a,9]



RESULTS AND DISCUSSION

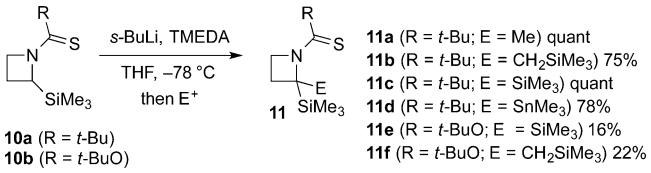
As noted above, formation of 2,2-disubstituted azacycles using α-lithiation−electrophile trapping methodology typically relies on the presence of an anion-stabilizing α-substituent to assist α-lithiation at the 2-position, and this strategy has previously been

Received: August 4, 2015
Published: September 24, 2015

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

used for the synthesis of 2,2-disubstituted azetidines using ester or aryl α-substituents.[10] Silyl groups are also known to stabilize α-anions, and there are a number of examples of an α-TMS group promoting regioselective synthesis of *N*-Boc-2,2-disubstituted pyrrolidines **1** at low temperature[4] (e.g., Scheme 1, R = $SiMe_3$, E = SMe[4b]). α-Lithiation−electrophile trapping of *N*-thiopivaloyl-2-(trimethylsilyl)azetidine (**10a**)[8a] was similarly found to cleanly generate 2,2-disubstituted azetidines **11a−d** in excellent yields (Scheme 3). These results, along with

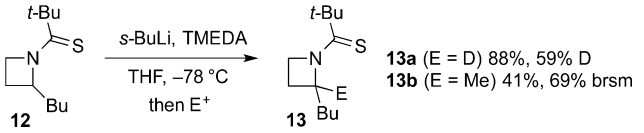
Scheme 3. α-Lithiation−Electrophile Trapping of *N*-Thiopivaloyl-2-(trimethylsilyl)azetidine (10)



the absence of rotamers for *N*-thiopivaloyl-2-(trimethylsilyl)-azetidine (**10a**) by ^{1}H NMR and the exclusive observation of NOEs between NCH_2 and *t*-Bu groups (Supporting Information, Figure S1), suggest that this substrate is present entirely as the *cis* rotamer shown in Scheme 3.[11] *N*-Botc-2-(trimethylsilyl)azetidine **10b**[9] (3.5:1 rotameric mixture at rt in $CDCl_3$) similarly gave 2,2-disubstituted azetidines **11e,f** with the electrophiles Me_3SiCl and Me_3SiCH_2Cl but in considerably lower yields [16% (19% brsm) and 22% (31% brsm), respectively].

Returning to study in more detail the more unusual effect of a 2-alkyl substituent on lithiation of *N*-thiopivaloylazetidine, we found that deuteration and also methylation of *N*-thiopivaloyl-2-butylazetidine (**12**)[8a] similarly gave electrophile incorporation only at the 2-position [Scheme 4, 88%, 59% D (by HRMS),

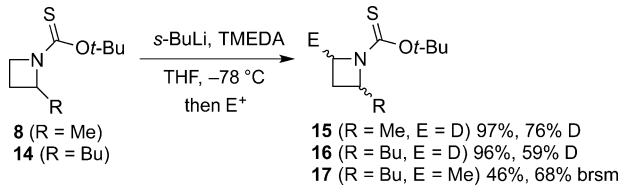
Scheme 4. α-Lithiation−Electrophile Trapping of *N*-Thiopivaloyl-2-butylazetidine (12)



and 41% yield (69% brsm) for methylation]. Compared with *N*-thiopivaloyl-2-(trimethylsilyl)azetidine (**10a**), both the 2-methyl and 2-butyl systems (**5** and **12**) exist as mixtures of rotamers (6:1 and 10:1, respectively, by ^{1}H NMR analysis in $CDCl_3$ at rt). Not unexpectedly, the dominant rotamer of *N*-thiopivaloyl-2-methylazetidine (**5**) was determined to be the less hindered *cis* rotamer (as shown in Scheme 2) on the basis of NOEs between the NCH_2 and *t*-Bu groups (Figure S2, Supporting Information), and this was supported by computational studies (see details below).[11] As no products were observed from α′-lithiation−electrophile trappings (i.e., at C-4) of the 2-methyl and 2-butyl systems **5** and **12**, then either the minor rotamers are not favorably orientated for lithiation or the C-4 lithiated species rapidly decompose[12] (rotamer interconversion, at the temperature and on the time scale of the lithiations, was excluded on the basis of barriers determined by NMR and by computation, as discussed below).

Our preliminary observation that *N*-Botc protection resulted in lithiation at the 4-position of 2-methylazetidine **8** (Scheme 2), rather than at the 2-position seen with the *N*-thiopivaloyl system, was probed in more detail through lithiation−deuteration studies. While essentially complete D incorporation had previously been observed with unsubstituted *N*-Botc-azetidine **7** after lithiation for 30 min at −78 °C (95% D, 90% mass recovery),[9] only 59% D (by HRMS analysis) was seen after this time with 2-methylated azetidine **8** (94% mass recovery); D incorporation rose to 76% (97% recovery) after 1 h at −78 °C (Scheme 5) but did not increase with further

Scheme 5. α′-Lithiation−Electrophile Trapping of *N*-Botc-2-alkylazetidines



lithiation time at this temperature. Almost complete D incorporation (91%) could be obtained on lithiation for 30 min at −78 °C followed by 15 min at −40 °C; however, anion stability was clearly an issue at this higher temperature with several unknown byproducts now being observed and significantly less azetidine recovered (50%). No deuteration at the 2-position was observed in any of these experiments. Similar results were obtained for deuteration and methylation of *N*-Botc-2-butylazetidine (**14**) (Scheme 5). An explanation for the observations at −78 °C is that the rotamers of *N*-Botc-2-alkylazetidines **8** and **14** (2.5:1 and 2.6:1, respectively, at rt, in $CDCl_3$) do not interconvert at this temperature and lithiation only occurs on the major rotamer; however, it then follows that the major rotamers must have *trans* orientation (shown in Scheme 5). Support for the lack of rotamer interconversion for *N*-Botc-2-methylazetidine **8** was found in barrier heights from NMR and computation studies described below. Support for the implication that the preferred α-methylazetidine rotamer switches from *cis* to *trans* in going from the *N*-thiopivaloyl to *N*-Botc groups was obtained from low-temperature NOESY studies on *N*-Botc-2-methylazetidine (**8**) in THF, which demonstrated NOEs from the *t*-Bu group to the NCH proton only for the major rotamer, whereas these were observed to the NCH_2 protons for the minor form (Figure S3, Supporting Information; low-temperature studies in toluene gave ambiguous results due to resonance coincidence of the NCH and NCH_2 groups of the major rotamer). This preference was also found in computational studies, as discussed below. Structurally related *N*-Boc-azetidine-2-carboxylic acid shows no preference for either rotameric form on the basis of two X-ray crystallographic reports: *cis* and *trans* amide-like conformations were separately obtained from the same solvent system.[13,14]

The above experimental observations on the site of azetidine lithiation being dependent on the *N*-protecting/activating group were intriguing, and we sought to understand them through NMR and computational studies. Heteroatom-directed lithiation (complex-induced proximity effect) is a well-established guiding principle, and a key assumption underpinning the analysis of the current chemistry is that the thiocarbonyl group plays such a role.[5,6,15] Knowledge of rotamer preferences and the energy barriers to rotamer interconversion in the current systems would therefore be crucial.

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

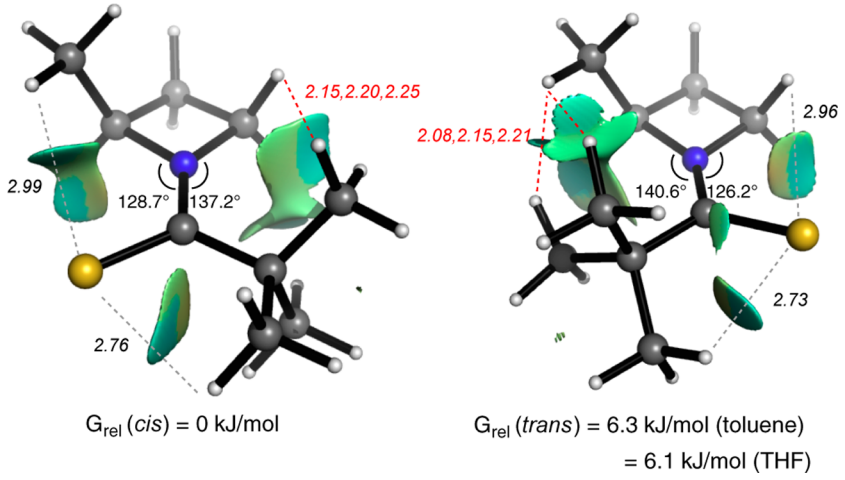


Figure 1. *Cis* and *trans* ground-state rotamers for *N*-thiopivaloyl-2-methylazetidine (**5**) [CPCM-M06-2X/6-311++G(d,p) computed G_{rel} at 25 °C]: distances shown in angstroms and steric contacts (<2.5 Å) highlighted in red. The NCI isosurface indicates the existence of nonbonding interactions.

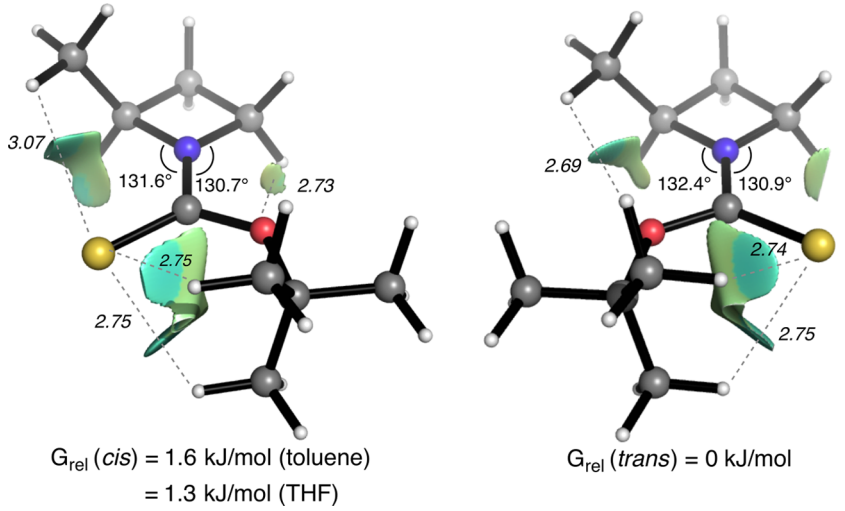
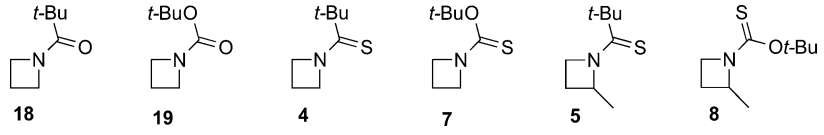


Figure 2. *Cis* and *trans* ground-state rotamers for *N*-Botc-2-methylazetidine (**8**) [CPCM-M06-2*X*/6-311++G(d,p) computed G_{rel} at 25 °C]: distances shown in Å. The NCI isosurface indicates the existence of nonbonding interactions.

The rotamer preferences of *N*-thiopivaloyl- and *N*-Botc-2-methylazetidine (**5**) and (**8**) were further studied through quantum chemical computations.[16] Geometry optimizations were performed at the density functional level of theory (wB97XD, M06-2X, B3LYP functionals were all examined with the 6-311++G(d,p) basis set) in the gas-phase and with the inclusion of solvation by toluene treated through the conductor-like polarizable continuum model (CPCM) with different solvent cavity definitions and the universal continuum solvation model, SMD. DFT results were corroborated by composite ab initio reference calculations employing the CBS-QB3 method.[17] For *N*-thiopivaloyl-2-methylazetidine (**5**), these calculations all identified the *cis* rotamer as the more stable, in agreement with the NOE studies noted previously (full comparison across all methods given in Table S1, Supporting Information). Quantitatively, the 5.7 kJ/mol free energy difference between *cis* and *trans* rotamers of azetidine **5** (from the 12.5:1 ratio by ^{1}H NMR in toluene-d_8 at 25 °C) lies in the middle of the range of the computed values (3.2 to 8.7 kJ/mol), with the M06-2X functional giving the closest agreement within 0.6 kJ/mol of experiment irrespective of solvation model chosen.[18] This conformational preference of azetidine **5** was not significantly altered in THF solvent (10.2:1 by ^{1}H NMR), and similarly, the relative stabilities were found to be perturbed by just 0.2 kJ/mol computationally.[19] As expected, DFT-optimized structures show close nonbonded contacts between the *tert*-butyl group and the *cis* oriented α-position of the azetidine, which lead to the rotamer where the CHMe group is oriented *cis* to the thiocarbonyl group being favored (Figure 1). In the higher energy *trans* rotamer, increased unfavorable steric interactions are found between the α-methyl and the *t*-Bu groups, with nonbonded H−H distances as close as 2.08 Å (c.f., sum of van der Waals' radii = 2.4 Å).[20] Greater repulsion in the *trans*-conformer is also evident from the more severely distorted exocyclic C−N−C bond angles shown in Figure 1 and also illustrated graphically by the noncovalent interaction index (NCI) isosurface:[21] the region in between the *tert*-butyl group and the azetidine is the largest in area, indicative that this interaction is a major conformational discriminant. This steric argument is also evident from space-filling models (Figure S23, Supporting Information). Despite the N atom being part of a 4-membered ring, conjugation between the nitrogen lone pair and the thiocarbonyl π-system results in a high degree of planarity at

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

Table 1. Comparison of Experimental and M06-2X/6-311++G(d,p) Computed Rotational Barriers for Azetidines 4,5,7,8,18, and 19 (NBO Wiberg Bond Orders and Populations Shown)



18 19 4 7 5 8

N-substituted azetidine	NMR $\Delta G^{\ddagger}$[a] (kJ/mol)	DFT $\Delta G^{\ddagger}$[b] (kJ/mol)	DFT-NMR $\Delta\Delta G^{\ddagger}$ (kJ/mol)	NMR $t_{1/2}$[c]	r_{C-N} (Å)	B.O.[d]	n_N occupancy[e]
N-pivaloyl (**18**)	57.6	57.2	−0.4	1231 s	1.34	1.18	1.70e
N-Boc (**19**)	58.5	62.1	3.6	4.9 h	1.34	1.15	1.72e
N-thiopivaloyl (**4**)	76.9	80.2	3.3	13.7 y	1.32	1.28	1.61e
N-Botc (**7**)	75.0	81.6	6.6	228 d	1.32	1.24	1.65e
N-thiopivaloyl-2-Me (**5**)	70.7	71.3	0.6	2.1 d	1.32	1.29	1.61e
N-Botc-2-Me (**8**)	75.0	75.8	0.8	116 d	1.33	1.23	1.65e

[a]Obtained from VT NMR study, value computed at 25 °C with errors estimated to be ±1.5 kJ/mol. [b]DFT optimizations using CPCM-M06-2X/6-311++G(d,p) at 25 °C. [c]Calculated half-lives (for major conformer of **5** and **8**) at −78 °C. [d]Calculated C−N Wiberg bond order. [e]NBO computed occupancy of the N lone pair in the planar ground state.

nitrogen,[11] and only a single very slightly pyramidalized stereoisomer of each ground-state rotamer exists [the pyramidalization, as judged by the vertical distance of the N atom from the plane defined by the three connected atoms, is 0.08 and 0.03 Å for the favored and disfavored rotamer, respectively at the CPCM-M06-2X/6-311++G(d,p) level of theory].

Unlike the dominant effect of the *t*-Bu group on the conformation of *N*-thiopivaloyl-2-methylazetidine (**5**), the presence of the oxygen atom "spacer" in *N*-Botc-2-methylazetidine (**8**) now results in the *t*-Bu group being effectively remote from the azetidine, such that steric interactions between these groups do not significantly influence the conformation (corresponding nonbonding interactions are absent from the NCI isosurface). Computed ground-state rotamers for azetidine **8** (Figure 2) both have S−C−O−CMe_3 dihedral angles of 6°, with bias of the *t*-Bu group toward the azetidine face bearing the methyl group. Exocyclic C−N−C angles are similar, and the distances between S and the *t*-Bu group are almost identical. There is no appreciable difference in either the C−N or C−S bonds of the thioamide, indicating little difference in π-conjugation between the two rotamers. A nonbonded interaction exists between the *t*-Bu group and the thiocarbonyl, although this feature is common to both structures (Figure 2, NCI analysis). Unsurprisingly, only a small conformational preference results: the ΔG ranges from 1.0 to 4.1 kJ/mol depending on the computational method, with the CPCM-M06-2X/6-311++G(d,p) level of theory (which describes the thiopivaloyl system **5** well) giving a value of 1.3−1.6 kJ/mol (for a full comparison of all methods examined, see Table S2, Supporting Information). The calculated rotamer free energy difference is close to 2.0 kJ/mol, determined from the 2.2:1 rotamer ratio seen by ^{1}H NMR in toluene-d_8 at 25 °C. A small energy difference makes a bold prediction of the identity of the major rotamer difficult; however, all DFT and ab initio methods consistently favor the same rotamer, in which the thiocarbonyl lies *trans* to the azetidine-Me group, opposite to that preferred for the thiopivaloyl protecting group but consistent with the NOEs noted earlier for azetidine **8**. This small conformational preference results from the alleviation of steric interactions between thiocarbonyl and methyl groups: natural bond orbital (NBO) contributions to the steric exchange energy (Pauli repulsion) between occupied orbitals are more unfavorable by 3.8 kJ/mol when the thiocarbonyl is *cis* to the methyl group. The presence of a weak stabilizing CH−O interaction (2.69 Å) involving the C-2 methyl group may be detected in the favored conformation, although its magnitude (0.4 kJ/mol by second-order perturbative estimates in the NBO basis) is insufficient to account for the overall conformational energy difference. As with the thiopivaloyl system **5** above, conjugation between the N-lone pair and the thiocarbonyl π-system yields essentially planar structures (pyramidalization of 0.09 and 0.13 Å for the favored and disfavored rotamers, respectively) without isomerism at nitrogen.

While the above NMR and computational analyses of rotamer preferences of *N*-thiopivaloyl- and *N*-Botc-2-methylazetidine (**5**) and (**8**) provide support and insight into the directed lithiation−electrophile trappings observed for these systems, they are only relevant if rotamer interconversions do not occur at the temperature and on the time scale of the lithiations. In carbamate (Boc)-directed lithiations of larger azacycles (pyrrolidines and piperidines), higher reaction temperatures than those found viable for the chemistry described here allowed rotamer interconversion on the lithiation time scale.[3b] While thioamides are known to have higher activation energies for N−C═S rotation compared to N−C═O in amides (due to the greater polarizability of S, allowing a greater charge transfer from N to S),[22] potential reduction of rotamer barriers due to the nitrogen being part of a 4-membered ring and the presence of the oxygen atom in the case of the thiocarbamate lent some initial uncertainty as to whether rotamer interconversion was possible in the current chemistry. So as to provide a broader view of the effect of various azetidine *N*-substituents on rotation barriers, *N*-pivaloyl- and *N*-Boc-azetidine (**18**)[8a] and (**19**)[23] were analyzed along with the thiopivaloyl and *N*-Botc systems **4**, **5**, **7**, and **8**. Variable-temperature (VT) ^{1}H NMR studies in toluene and line-shape analysis were used to obtain approximate rotational activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) from which activation energy ($\Delta G^{\ddagger}$) [and half-life ($t_{1/2}$)] values were calculated (Supporting Information) and compared with those obtained computationally (Table 1). The NMR-determined barriers to thiopivaloyl and Botc rotation in the 2-methylazetidines **5** and **8** at 25 °C (70.7 and 75.0 kJ/mol, respectively) indicate rotation half-lives of 0.3 and 1.6 s; however, these extend to 2.1 and 116 days at −78 °C, implying that rotamer interconversion is not significant under the lithiation conditions.

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

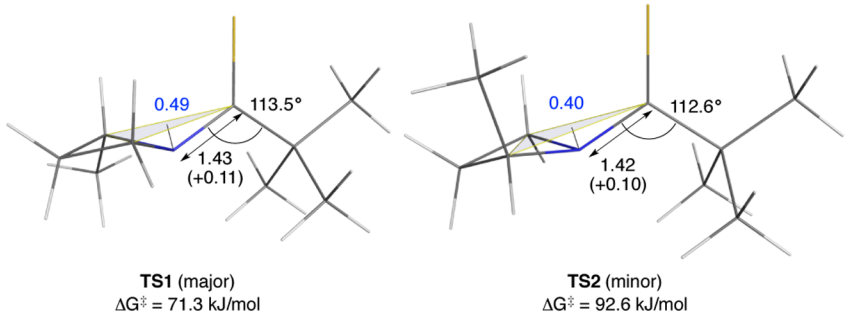


Figure 3. Rotation TS structures found for *N*-thiopivaloyl-2-methylazetidine (**5**) [CPCM-M06-2X/6-311++G(d,p) computed free energies at 25 °C]. Interatomic distances (black) and pyramidalization (blue) are shown in angstroms. Parentheses indicate bonding changes relative to the planar ground state.

The transition-state (TS) free energies were determined for the most stable structure corresponding to rotation about the C−N bond for the six azetidines in Table 1 and are concordant with experimental values obtained from VT-NMR. Based on the success of M06-2*X*/6-311++G(d,p) calculations in reproducing ground state rotamer energy differences of **5** and **8**, we adopted this level of theory in subsequent studies. Good-to-excellent quantitative accuracy was achieved: the mean unsigned error (MUE) across the six computed barrier heights with respect to experiment is 2.5 kJ/mol, well within the expected accuracy range for the M06-2X functional (a MUE of 5.1 kJ/mol over 76 diverse barrier heights has been reported).[24] Up to four TSs were located for the rotation of each azetidine, and the most stable structure was used to evaluate the barrier, relative to the more stable planar conformer. In common with simple amides and thioamides, *N*-pivaloyl- and *N*-Boc-azetidines **18** and **19** show substantially lower activation barriers (by nearly 20 kJ/mol) than their thiocarbonyl counterparts **4** and **7**. The computed C−N bond lengths and bond orders in Table 1 illustrate why this is so: the extent of $n_N - \pi^*_{CO}$ delocalization in the ground state structures with a carbonyl group is smaller than for the analogous $n_N - \pi^*_{CS}$. Out-of-plane rotation is thus more facile for the amide and carbamate functional groups since the C−N bond order is smaller in the ground state (the degree of conjugation is lower). As the C−N bond is rotated and conjugation is broken, the calculated N lone pair occupancy increases and orbital energy is lowered: in fact, for all TSs computed in the present study there is a good linear correlation (R^2 = 0.89) between the activation barrier and the extent to which the N lone pair energy is lowered at the TS geometry (Figure S24, Supporting Information).[25]

The (symmetry breaking) exocyclic N−C rotation of the unsubstituted azetidines (**4**, **7**, **18**, and **19**), leads to a loss of conjugation between the nitrogen lone pair and the π^* of the carbonyl/thiocarbonyl and the possibility of two distinct TSs that differ due to the direction of nitrogen pyramidalization; the structures found computationally for each of these systems are discussed in detail in the Supporting Information. Additionally, for *N*-thiopivaloyl- and *N*-Botc-2-methylazetidine (**5**) and (**8**), rotation about the N−C bond in each sense is not equivalent, which in combination with the sense of N-pyramidalization creates the possibility for four distinct TS structures for rotamer interconversion. Two such TSs were located for *N*-thiopivaloyl-2-methylazetidine (**5**) (Figure 3), in which the N lone pair lies antiperiplanar to the thiocarbonyl C−S σ^* orbital. In the more stable **TS1**, the 2-methyl substituent adopts an equatorial position on the puckered azetidine ring, while it is axially oriented in the less favorable structure. Neither conformation with the N (sp^3-type) lone pair antiperiplanar to the *t*-Bu group could be found, since these induce extremely unfavorable steric interactions and hyperconjugation is reduced. We were able to locate such a structure for unsubstituted thiopivaloyl system **4**, where the energetic penalty of such unfavorable interactions resulted in a $\Delta\Delta G^{\ddagger}$ relative to the more stable structure of 42.7 kJ/mol (Supporting Information), and thus, we can be confident that such a TS does not contribute to the rate of rotation for **5**. The computed activation barrier of **TS1** (71.3 kJ/mol) is in excellent agreement (within 0.6 kJ/mol) with the NMR value, 70.7 kJ/mol. In the less stable **TS2** the axial methyl group leads to a 1,3-diaxial interaction with a C−H on the azetidine ring, which acts to restrict the extent of N-pyramidalization as highlighted in Figure 3.

All four possible TSs were found for the exocyclic C−N rotation of *N*-Botc-2-methylazetidine (**8**) (Figure 4), and their

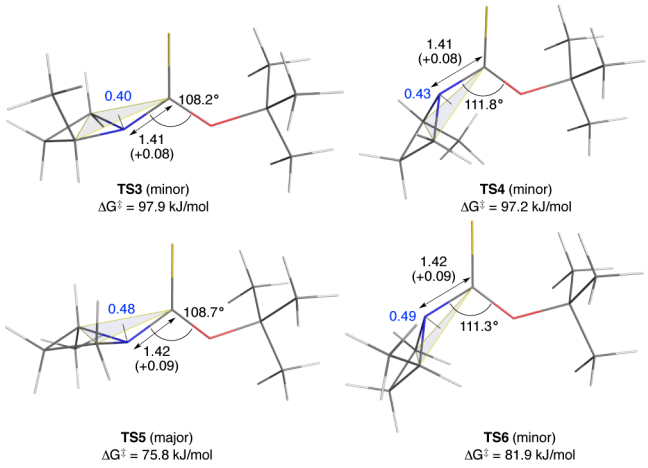


Figure 4. Rotation TS structures found for *N*-Botc-2-methylazetidine (**8**) [CPCM-M06-2X/6-311++G(d,p) computed free energies at 25 °C]. Interatomic distances (black) and pyramidalization (blue) are shown in Å. Parentheses indicate bonding changes relative to the planar ground state.

relative stabilities may be reasoned with both steric and electronic arguments. Conformations in which the methyl group is axially oriented with respect to the puckered azetidine ring (**TS3** and **TS4**) experience 1,3-diaxial strain, raising the energy of these TSs by ∼20 kJ/mol relative to their equatorial counterparts. The *t*-Bu exerts little steric effect upon the conformational preference, and thus, the most stable TS (with an equatorial methyl group) is **TS5** in which the N

DOI: 10.1021/acs.joc.5b01804
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pyramidalization is such that its lone pair is oriented antiperiplanar to the thiocarbonyl C−S σ^* orbital, a superior acceptor to C−O σ^*. As above, the rotational barrier computed for the most stable TS (75.8 kJ/mol) lies in close agreement with the experimental value of 75.0 kJ/mol, lending credence to the computation. The lower rotational barrier of **5** relative to **4** obtained from both experiment and theory may be attributable to greater steric strain present in the planar ground state and its relief in the rotational TS.

CONCLUSIONS

The ability to selectively substitute different C−H bonds in a substrate, through different removable activating groups attached at a common position on the substrate, contributes to flexibility in molecule construction (diversity-oriented synthesis). The work described here provides an example of this in substituted azetidine synthesis, where the latter also constitutes an area of considerable current interest. *N*-Thiocarbonyl attachment on 2-alkyl-substituted azetidines directs lithiation−electrophile trapping to either the 2- or 4-position depending on whether the thiocarbonyl substituent is *tert*-butyl or *tert*-butoxy, respectively. ^{1}H NMR and computational studies on these substrates indicate that rotamer interconversion is not significant under the lithiation conditions, so that the origin of the regiodivergent reactivity likely lies in different rotamer preferences (*cis* for the thioamide and *trans* for the *O*-alkyl thiocarbamate); the computational studies also provide further insight into the factors influencing rotamer preference and, more generally, the magnitude of rotational barriers of a range of thiocarbonyl-substituted azetidines. The *N*-thiopivaloyl α-alkylazetidines show a strong *cis* rotamer preference, as this avoids close *t*-Bu-α-alkyl nonbonded interactions present in the *trans* rotamer. In contrast, the *N*-(*tert*-butoxythiocarbonyl)-α-alkylazetidines show a less-prominent and opposite rotamer bias, where alleviation of thiocarbonyl−α-alkyl nonbonded interactions and a weak CH−O stabilizing interaction have been identified as contributing factors to the *trans*-rotamer preference. The exploration of the *N*-thiocarbonyl activating groups in differential C−H manipulation on other substrates, together with the use of chiral ligands to influence stereoselectivities in the substitution reactions,[9] are attractive areas for future investigations.

EXPERIMENTAL SECTION

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of nitrogen or argon. THF was degassed and dried over activated alumina under nitrogen.[26] TMEDA was distilled over CaH_2; MeI was passed through basic alumina immediately before use; Me_3SiCl was distilled and passed through basic alumina; all other reagents were used as received. *s*-BuLi was titrated on arrival and periodically thereafter using 2-propanol solution in toluene with 0.2% 1,10-phenanthroline indicator titration solution for quantitative analysis of BuLi. Thin-layer chromatography (TLC) was carried out on aluminum-backed plates precoated with silica (0.2 mm, 60 F254 nm), which were visualized with UV light (λ_{max} = 254 nm) and/or developed with basic potassium permanganate solution with heating. Column chromatography was carried out on Si gel (43−63 μm) in the solvent systems indicated, applying head pressure by means of a low pressure nitrogen line (0.1−0.3 atm). Petroleum ether refers to the fraction boiling between 30 and 40 °C. Melting points are uncorrected. Infrared spectra were recorded neat, and the intensity of the peaks are reported as s, m, w, and br, denoting strong, medium, weak, and broad, respectively. Standard ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$, THF-d_8, or toluene-d_8. ^{13}C DEPT, COSY, and HSQC spectra were used to aid structure assignments. Data are expressed as chemical shifts (δ) in parts per million (ppm) relative to $CDCl_3$ (^{1}H δ 7.27 ppm, ^{13}C δ 77.0 ppm, respectively), THF-d_8 (^{1}H δ 3.58 ppm), or toluene-d_8 (^{1}H δ 6.98 ppm) as the internal standard on the δ scale. The multiplicity of each signal is reported as s, d, t, quin, and m, denoting singlet, doublet, triplet, quintet, and multiplet, respectively. Proton-coupling constants J are reported to the nearest 0.1 Hz. Discernible NMR signals for minor rotamers or diastereomers are indicated in parentheses. High-resolution mass spectra were obtained via a TOF mass analyzer by field ionization (FI), or by electrospray ionization (ESI) using tetraoctylammonium bromide or sodium dodecyl sulfate as the lock mass; values are quoted as a ratio of mass to charge (m/z) in daltons, and relative intensities of assignable peaks observed are quoted as a percentage value of the base peak.

1-(Azetidin-1-yl)-2,2-dimethylpropane-1-thione (4). *N*-Thiopivaloylazetidine **4** was prepared according to the literature procedure:[8a] ^{1}H NMR (500 MHz, toluene-d_8) δ 3.93 (t, J = 7.9 Hz, 2H, NCH_2), 3.64 (t, J = 7.9 Hz, 2H, NCH_2), 1.44−1.38 (m, 2H, CH_2), 1.22 (s, 9H, $C(CH_3)_3$). All other data were consistent with the literature.[8a]

2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (5). *N*-Thiopivaloyl-2-methylazetidine **5** was prepared according to the literature procedure:[8a] ^{1}H NMR (500 MHz, toluene-d_8) (12.0:1 rotamer mixture by analysis of $NCHCH_3$ signals at 1.42 and 1.01) δ 4.69−4.62 (4.06−4.01) (m, 1H, NCH), 3.79−3.61 (4.00−3.95) (m, 2H, NCH_2), 1.78−1.71 (m, 1H, $NCHCHH'$), 1.42 (1.01) (d (br s), J = 6.2 Hz, 3H, $NCHCH_3$), 1.22 (1.30) (s, 9H, $C(CH_3)_3$), 1.17−1.11 (m, 1H, $NCHCHH'$); ^{1}H NMR (500 MHz, THF-d_8) (10.2:1 rotamer mixture by analysis of $NCHCH_3$ signals at 1.61 and 1.52) δ 4.78−4.71 (4.84−4.80) (m, 1H, NCH), 4.58−4.53 (4.16−4.10) (m, 1H, $NCHH'$), 4.46−4.41 (4.07−4.03) (m, 1H, $NCHH'$), 2.51−2.42 (m, 1H, $NCHCHH'$), 1.82−1.76 (m, 1H, $NCHCHH'$), 1.52 (1.61) (d, J = 6.3 Hz, 3H, $NCHCH_3$), 1.28 (1.35) (s, 9H, $C(CH_3)_3$). All other data were consistent with the literature.[8a]

***O-tert*-Butyl Azetidine-1-carbothioate (7).** *N*-Botc-azetidine **7** was prepared according to the literature procedure:[9] ^{1}H NMR (500 MHz, toluene-d_8) δ 3.77 (t, J = 7.6 Hz, 2H, NCH_2), 3.43 (t, J = 7.6 Hz, 2H, NCH_2), 1.61 (s, 9H, $C(CH_3)_3$), 1.31 (quin, J = 7.6 Hz, 2H, CH_2). All other data were consistent with the literature.[9]

***O-tert*-Butyl 2-methylazetidine-1-carbothioate (8).** *N*-Botc-2-methylazetidine **8** was prepared according to the literature procedure:[9] ^{1}H NMR (500 MHz, toluene-d_8) (2.2:1 rotamer mixture by analysis of NCH signals at 4.34−4.27 and 3.91−3.85) δ 3.91−3.85 (4.34−4.27) (m, 1H, NCH), 3.80−3.71 (3.58−3.45) (m, 2H, NCH_2), 1.68−1.54 (m, 1H, $NCHCHH'$), 1.59 (1.60) (s, 9H, $C(CH_3)_3$), 1.17−1.05 (m, 1H, $NCHCHH'$); 1.09 (1.40) (d, J = 6.3 Hz, 3H, $NCHCH_3$); ^{1}H NMR (500 MHz, THF-d_8) (2:1 rotamer mixture by analysis of $NCHCH_3$ signals at 1.49 and 1.40) δ 4.36−4.29 (4.46−4.36) (m, 1H, NCH), 3.97−3.85 (m, 2H, NCH_2), 2.36−2.24 (m, 1H, $NCHCHH'$), 1.76−1.68 (m, 1H, $NCHCHH'$), 1.61 (1.60) (s, 9H, $C(CH_3)_3$), 1.40 (1.49) (d, J = 6.3 Hz, 3H, $NCHCH_3$). All other data were consistent with the literature.[9]

General Procedure A: α-Deprotonation−Electrophile Trapping of *N*-Thiopivaloyl-2-substituted Azetidine (10a or 12). A solution of 2,2-dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**10a**)[8a] (1 equiv) or 1-(2-butylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**12**)[8a] (1 equiv) in THF (8 mL/mmol **10a**/**12**) was cooled to −78 °C (acetone/dry ice) before addition of TMEDA (2.4 equiv). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was then added rapidly in one portion (1 mL in <2 s). The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (2−3 equiv). The reaction mixture was stirred for 20 min at −78 °C, warmed to rt over 10 min, stirred at rt for a further 20 min, quenched with aq HCl (1 M, 10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

*2,2-Dimethyl-1-(2-methyl-2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**11a**).* 2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)-

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

propane-1-thione (**10a**)[8a] (80 mg, 0.35 mmol) and MeI (65 μL, 1.05 mmol) were used following general procedure A, resulting in a white solid, 2,2-disubstituted azetidine **11a** (85 mg, quant): R_f 0.59 (petroleum ether/Et_2O 9:1); mp 88−89 °C; IR (neat/cm^{-1}) 2964 m, 2945 m, 2901 w, 1480 s, 1459 s, 1432 s, 1393 w, 1360 m, 1244 s, 1143 w, 1125 w, 1104 w, 1079 w, 959 m, 861 s, 829 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63−4.56 (m, 1H, NC*H*H′), 4.40−4.34 (m, 1H, NCH*H*′), 2.40−2.33 (m, 1H, NCH_2CHH'), 1.83−1.77 (m, 1H, NCH_2CHH'), 1.74 (s, 3H, NC_qCH_3), 1.31 (s, 9H, $C(CH_3)_3$), 0.17 (s, $^2J_{29Si-H}$ = 7 Hz, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2 (C═S), 69.6 (NC_q), 54.8 (NCH_2), 42.7 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$), 25.8 (NCH_2CH_2), 20.6 (NC_qCH_3), − 1.6 ($Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{12}H_{25}NNaS^{28}Si$ 266.1369 $[M + Na]^+$, found 266.1368.

*2,2-Dimethyl-1-(2-(trimethylsilyl)-2-((trimethylsilyl)methyl)-azetidin-1-yl)propane-1-thione (**11b**).* 2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**10a**)[8a] (61 mg, 0.27 mmol) and Me_3SiCH_2Cl (113 μL, 0.81 mmol) were used following general procedure A. Purification of the resulting yellow solid by column chromatography (SiO_2, 2−4% Et_2O/petroleum ether) gave a white solid, 2,2-disubstituted azetidine **11b** (63 mg, 75%): R_f 0.58 (petroleum ether/Et_2O 9:1); mp 87−88 °C; IR (neat/cm^{-1}) 2967 w, 2949 w, 2890 w, 1464 m, 1444 s, 1315 w, 1126 m, 1098 w, 995 m, 927 w, 831 s, 757 m, 699 w, 681 w, 670 w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58−4.51 (m, 1H, NC*H*H′), 4.40−4.34 (m, 1H, NCH*H*′), 2.29 (ddd, *J* = 11.6, 10.2, 6.3 Hz, 1H, C*H*H′), 2.20 (d, *J* = 14.7 Hz, 1H, C*H*H′$Si(CH_3)_3$), 2.05 (ddd, *J* = 11.6, 10.2, 6.3 Hz, 1H, CH*H*′), 1.31 (s, 9H, $C(CH_3)_3$), 1.19 (d, *J* = 14.7 Hz, 1H, CH*H*′$Si(CH_3)_3$), 0.17 (s, $^2J_{29Si-H}$ = 7 Hz, 9H, $Si(CH_3)_3$), 0.11 (s, $^2J_{29Si-H}$ = 6 Hz, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3 (C═S), 72.6 (NC_q), 55.4 (NCH_2), 43.0 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 24.4 (NCH_2CH_2), 22.1 ($CH_2Si(CH_3)_3$), 0.8 (J_{29Si-C} = 51 Hz, $Si(CH_3)_3$), − 0.9 (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{15}H_{33}NNaS^{28}Si_2$ 338.1764 $[M + Na]^+$, found 338.1750.

*1-(2,2-Bis(trimethylsilyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**11c**).* 2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione (**10a**)[8a] (80 mg, 0.35 mmol) and Me_3SiCl (133 μL, 1.05 mmol) were used following general procedure A, resulting in a white solid, 2,2-disubstituted azetidine **11c** (105 mg, quant): R_f 0.72 (*n*-hexane/EtOAc 9:1); mp 97−99 °C; IR (neat/cm^{-1}) 2965 w, 2160 w, 1978 w, 1463 s, 1396 w, 1364 w, 1259 m, 1246 s, 1126 m, 1067 w, 1012 w, 1003 w, 951 w, 902 w, 832 s, 754 m, 862 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41−4.37 (m, 2H, NCH_2), 2.25−2.21 (m, 2H, NCH_2CH_2), 1.31 (s, 9H, $C(CH_3)_3$), 0.22 (s, 18H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0 (C═S), 66.7 (NC_q), 55.9 (NCH_2), 42.3 ($C(CH_3)_3$), 29.8 ($C(CH_3)_3$), 20.1 (NCH_2CH_2), 0.14 (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{14}H_{31}NNaS^{28}Si_2$ 324.1608 $[M + Na]^+$, found 324.1598.

*2,2-Dimethyl-1-(2-(trimethylsilyl)-2-(trimethylstannyl)azetidin-1-yl)propane-1-thione (**11d**).* 2,2-Dimethyl-1-(2-(trimethylsilyl)-azetidin-1-yl)propane-1-thione (**10a**)[8a] (80 mg, 0.35 mmol) and Me_3SnCl (139 mg, 0.70 mmol) were used following general procedure A. Purification of the resulting white solid (SiO_2, 2% Et_2O/petroleum ether) gave a white solid, 2,2-disubstituted azetidine **11d** (107 mg, 78%): R_f 0.72 (petroleum ether/Et_2O 9:1); mp 100−101 °C; IR (neat/cm^{-1}) 2969 s, 2889 m, 1480 s, 1466 s, 1442 m, 1363 w, 1244 s, 1179 w, 1125 m, 1062 w, 866 m, 834 s, 754 s, 724 w, 675 w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59−4.42 (m, 2H, NCH_2), 2.44−2.30 (m, 2H, NCH_2CH_2), 1.33 (s, 9H; $C(CH_3)_3$), 0.17 (s, $^2J_{119Sn-H}$ = 52 Hz, $^2J_{117Sn-H}$ = 50 Hz, 9H, $Sn(CH_3)_3$), 0.15 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8 (C═S), 68.0 ($J_{119Sn-C}$ = 302 Hz, $J_{117Sn-C}$ = 289 Hz, J_{29Si-C} = 51 Hz, NC_q), 56.5 (NCH_2), 42.1 ($C(CH_3)_3$), 29.9 ($C(CH_3)_3$), 21.5 (NCH_2CH_2), − 0.7 (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$), − 5.7 ($J_{119Sn-C}$ = 327 Hz, $J_{117Sn-C}$ = 312 Hz, $Sn(CH_3)_3$); HRMS (ESI^+) calcd for $C_{14}H_{31}NNaS^{28}Si^{120}Sn$ 416.0861 $[M + Na]^+$, found 416.0850.

*1-(2-Butyl-2-($^2H_1$)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**13a**).* 1-(2-Butylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**12**)[8a] (33 mg, 0.16 mmol) and CD_3OD (19 μL, 0.46 mmol) were used following general procedure A. Purification of the resulting colorless oil by column chromatography (SiO_2, 10% Et_2O/petroleum ether) gave a colorless oil, 2,2-disubstituted azetidine **13a** (29 mg, 88% mass recovery, 59% D by FI HRMS analysis): R_f 0.22 (petroleum ether/Et_2O 9:1); IR (neat/cm^{-1}) 2958 m, 2925 m, 2871 w, 1457 m, 1426 s, 1394 w, 1362 m, 1256 m, 1140 m, 1000 m; ^{1}H NMR (500 MHz, $CDCl_3$) (5.8:1 rotamer ratio by analysis of NCH signals in the 4.78−4.64 region) δ 4.78−4.73 (4.69−4.64) (m, 0.6H, NCH), 4.52−4.46 (4.24−4.15) (m, 1H, NC*H*H′), 4.42−4.36 (4.24−4.15) (m, 1H, NCH*H*′), 2.49−2.34 (m, 2H, $CH_2(CH_2)_2CH_3$), 1.95−1.88 (m, 1H, NCH_2CHH'), 1.80−1.73 (m, 1H, NCH_2CHH'), 1.39−1.23 (m, 13H, $C(CH_3)_3$ and $(CH_2)_2CH_3$), 0.91 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamer mixture) δ 209.60 (C═S), 209.56 (C═S), 68.7 (69.7) (NCH), 68.3 (T, *J* = 22.9 Hz, NCD), 55.83 (54.27) (NCH_2), 55.82 (54.25) (NCH_2), 43.30 (43.98) ($C(CH_3)_3$), 30.3 ($CH_2(CH_2)_2CH_3$), 30.1 (30.9) ($CH_2(CH_2)_2CH_3$), 29.6 ($C(CH_3)_3$), 25.73 (26.23) (CH_2CH_3), 25.71 (26.25) (CH_2CH_3), 22.5 (22.3) ($CH_2CH_2CH_3$), 21.2 (20.9) (CH_2), 21.0 (20.8) (CH_2), 14.04 (13.95) (CH_2CH_3); HRMS (FI^+) calcd for $C_{12}H_{22}DNS$ 214.1614 $[M]^+$, found 214.1611.

*1-(2-Butyl-2-methylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**13b**).* 1-(2-Butylazetidin-1-yl)-2,2-dimethylpropane-1-thione (**12**)[8a] (75 mg, 0.35 mmol) and MeI (66 μL, 1.1 mmol) were used following general procedure A. Purification of the resulting pale yellow oil by column chromatography (SiO_2, 2−4% Et_2O/petroleum ether) gave a colorless oil, 2,2-disubstituted azetidine **13b** (33 mg, 41%, 69% brsm): R_f 0.34 (petroleum ether/Et_2O 9:1); IR (neat/cm^{-1}) 2958 m, 2927 m, 2872 w, 1739 w, 1461 s, 1418 s, 1363 m, 1262 w, 1119 s, 995 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49−4.44 (m, 1H, NC*H*H′), 4.40−4.35 (m, 1H, NCH*H*′), 2.53−2.47 (m, 1H, C*H*H′$CH_2CH_2CH_3$), 2.23−2.17 (m, 1H, C*H*H′CH_2N), 1.96−1.90 (m, 1H, CH*H*′CH_2N), 1.83−1.77 (m, 1H, CH*H*′$CH_2CH_2CH_3$), 1.77 (s, 3H, CH_3), 1.40−1.23 (m, 4H, $CH_2CH_2CH_3$), 1.29 (s, 9H, $(CH_3)_3$), 0.91 (t, *J* = 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7 (C═S), 77.3 ($NCCH_3$), 54.6 (NCH_2), 43.6 ($C(CH_3)_3$), 35.9 ($CH_2CH_2CH_2CH_3$), 29.3 ($C(CH_3)_3$), 27.8 (CH_2), 25.8 ($CH_2CH_2CH_3$), 23.8 ($NCCH_3$), 22.8 (CH_2CH_3), 14.1 (CH_2CH_3); HRMS (ESI^+) calcd for $C_{13}H_{25}NNaS$ 250.1600 $[M + Na]^+$, found 250.1597.

General Procedure B: α′-Deprotonation−electrophile Trapping of *O-tert*-Butyl 2-(Trimethylsilyl)azetidine-1-carbothioate (10b).[9] A solution of *O-tert*-butyl 2-(trimethylsilyl)azetidine-1-carbothioate (**10b**)[9] (1 equiv) in THF (8 mL/mmol) was cooled to −78 °C (acetone/dry ice) before the addition of TMEDA (2.4 equiv). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was then added dropwise (200 μL/min). The reaction mixture was stirred for 30 min at −78 °C before the addition of the electrophile (3 equiv). The reaction mixture was stirred for 20 min at −78 °C, warmed to rt over 10 min, stirred at rt for a further 20 min, quenched with satd aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

*O-tert-Butyl 2,2-bis(trimethylsilyl)azetidine-1-carbothioate (**11e**).* *O-tert*-Butyl 2-(trimethylsilyl)azetidine-1-carbothioate (**10b**)[9] (80 mg, 0.33 mmol) and Me_3SiCl (124 μL, 0.98 mmol) were used following general procedure B. Purification of the resulting colorless oil by column chromatography (SiO_2, 2−50% Et_2O/petroleum ether) gave a colorless oil, 2,2-disubstituted azetidine **11e** (16 mg, 16%, 19% brsm): R_f 0.81 (petroleum ether/EtOAc 19:1); IR (neat/cm^{-1}) 2961 w, 2360 w, 2342 w, 1481 s, 1445 s, 1390 w, 1365 w, 1274 m, 1249 s, 1223 m, 1137 s, 1007 m, 937 m, 884 w, 838 s, 757 w, 735 w, 689 w; ^{1}H NMR (400 MHz, $CDCl_3$) (10:1 mixture of rotamers by analysis of $Si(CH_3)_3$ signals at 0.24 and 0.15) δ 4.07−4.04 (m, 2H, NCH_2), 2.17−2.14 (m, 2H, NCH_2CH_2), 1.73 (1.58) (s, 9H, $C(CH_3)_3$), 0.15 (0.24) (s, $^2J_{29Si-H}$ = 6 Hz, 18H, $Si(CH_3)_3 \times 2$); ^{13}C NMR (100 MHz, $CDCl_3$) (rotamer mixture) δ 182.1 (C═S), 85.5 ($C(CH_3)_3$), 61.7 (C_q-Si), 52.3 (50.6) (NCH_2), 29.0 (28.7) ($C(CH_3)_3$), 19.6 ($NCHCH_2$), − 1.83 (−0.68) (J_{29Si-C} = 52 Hz, $Si(CH_3)_3 \times 2$); HRMS (ESI^+) calcd for $C_{14}H_{31}NNaOS^{28}Si_2$ 340.1557 $[M + Na]^+$, found 340.1551.

*O-tert-Butyl 2-(Trimethylsilyl)-2-((trimethylsilyl)methyl)azetidine-1-carbothioate (**11f**).* *O-tert*-Butyl 2-(trimethylsilyl)azetidine-1-carbothioate (**10b**)[9] (44 mg, 0.18 mmol) and Me_3SiCH_2Cl (68 μL, 0.49 mmol) were used following general procedure B. Purification of the resulting colorless oil by column chromatography (SiO_2, 2% Et_2O/

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

petroleum ether) gave a colorless oil, 2,2-disubstituted azetidine **11f** (13 mg, 22%, 31% brsm): R_f 0.45 (10% Et_2O/petroleum ether); IR (neat/cm^{-1}) 2953 w, 2897 w, 1479 s, 1444 s, 1391 w, 1365 w, 1278 m, 1248 s, 1198 s, 1144 w, 963 w, 836 s, 736 w, 736 w, 691 w; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02−3.95 (m, 1H, NC*H*H′), 3.90−3.83 (m, 1H, NCH*H*′), 2.07 (t, J = 7.8 Hz, 2H, CH_2), 1.69 (s, 9H, $C(CH_3)_3$), 1.58 (d, J = 15.1 Hz, 1H, C*H*H′$Si(CH_3)_3$), 0.93 (d, J = 15.1 Hz, 1H, CH*H*′$Si(CH_3)_3$), 0.12 (s, $^2J_{29Si-H}$ = 6 Hz, 9H, $Si(CH_3)_3$), 0.11 (s, $^2J_{29Si-H}$ = 6 Hz, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4 (C═S), 85.0 ($C(CH_3)_3$), 66.9 (NC_q), 49.1 (NCH_2), 28.9 ($C(CH_3)_3$), 23.4 (CH_2), 22.8 ($CH_2Si(CH_3)_3$), 0.42 (J_{29Si-C} = 51 Hz, $Si(CH_3)_3$), −3.25 (J_{29Si-C} = 52 Hz, $Si(CH_3)_3$); HRMS (ESI^+) calcd for $C_{15}H_{33}NNaOS^{28}Si_2$ 354.1717 $[M + Na]^+$, found 354.1711.

General Procedure C: α′-Deprotonation−electrophile Trapping of *N*-Botc-2-alkylazetidine (8 or 14). A solution of *O-tert*-butyl 2-methylazetidine-1-carbothioate (**8**)[9] (1 equiv) or *O-tert*-butyl 2-butylazetidine-1-carbothioate (**14**)[9] (1 equiv) in THF (6 mL/mmol **8**/**14**) was cooled to −78 °C (acetone/dry ice) before the addition of TMEDA (2.4 equiv). *s*-BuLi (1.3 M in cyclohexane/hexane, 1.3 equiv) was then added dropwise (~200 μL/min). The reaction mixture was stirred at this temperature (−78 °C) for a lithiation time of 30 min or 1 h before the addition of the electrophile (3 equiv). The reaction mixture was stirred for 20 min at −78 °C, warmed to rt over 10 min, stirred at rt for a further 20 min, quenched with satd aq NH_4Cl (10 mL), and extracted with Et_2O (4 × 10 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

*O-tert-Butyl 2-Methyl-4-($^2H_1$)azetidine-1-carbothioate (**15**) by a Modified Procedure C.* *O-tert*-Butyl 2-methylazetidine-1-carbothioate (**8**)[9] (36 mg, 0.19 mmol) and CD_3OD (23 μL, 0.57 mmol) were used following a modified general procedure C: after the dropwise addition of *s*-BuLi (1.3 M in cyclohexane/hexane, 192 μL, 0.25 mmol), the reaction mixture was stirred for 30 min at −78 °C, warmed to −40 °C over 15 min, and recooled to −78 °C before addition of CD_3OD (23 μL, 0.57 mmol). Purification of the resulting very pale yellow oil by column chromatography (SiO_2, 10% Et_2O/petroleum ether) gave a colorless oil, 2,4-disubstituted azetidine **15** (18 mg, 50% mass recovery, 91% D by FI HRMS analysis), as a ~ 1:1 mixture of inseparable diastereomers: R_f 0.29 (petroleum ether/EtOAc 19:1); IR (neat/cm^{-1}) 2967 w, 2928 w, 1469 s, 1436 s, 1391 w, 1365 w, 1342 w, 1274 s, 1140 s, 1005 w, 969 w, 955 w, 825 w; ^1H NMR (500 MHz, $CDCl_3$) (2.1:1 rotamer mixture by analysis of NCH signals in the 4.57−4.34 region) δ 4.40−4.34 (4.57−4.50) (m, 1H, NC*H*CH_3), 4.06−3.89 (m, 1H, NCHD), 2.39−1.72 (m, 2H, NCHC*H*$_2$), 1.65 (1.64) (s, 9H, $C(CH_3)_3$), 1.43 (1.57) (d, J = 6.0 Hz, 3H, NCHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamer mixture) δ 185.3 (C═S), 84.7 (84.5) ($C(CH_3)_3$), 59.9 (61.0) (NCH), 48.7 (48.8) (T, J = 22.9 Hz, CHD), 28.5 ($C(CH_3)_3$), 22.2 (22.7) ($NCHCH_2$), 20.6 (19.8) ($NCHCH_3$); HRMS (FI^+) calcd for $C_9DH_{16}NOS$ 188.1094 $[M]^+$, found 188.1094.

*O-tert-Butyl 2-Methyl-4-($^2H_1$)azetidine-1-carbothioate (**15**).* *O-tert*-Butyl 2-methylazetidine-1-carbothioate (**8**)[9] (36 mg, 0.19 mmol) and CD_3OD (23 μL, 0.57 mmol) were used following general procedure C with a lithiation time of 1 h. Purification of the resulting very pale yellow oil by column chromatography (SiO_2, 10% Et_2O/petroleum ether) gave a colorless oil, 2,4-disubstituted azetidine **15** (35 mg, 97% mass recovery, 76% D by FI HRMS analysis), as a ~ 1:1 mixture of inseparable diastereomers. Data as above.

*O-tert-Butyl 2-Butyl-4-($^2H_1$)azetidine-1-carbothioate (**16**).* *O-tert*-Butyl 2-butylazetidine-1-carbothioate (**14**)[9] (23 mg, 0.1 mmol) and CD_3OD (12 μL, 0.3 mmol) were used following general procedure C with a lithiation time of 1 h. Purification of the resulting colorless oil by column chromatography (SiO_2, 10% Et_2O/petroleum ether) gave a colorless oil, *N*-Botc-2,4-disubstituted azetidine **16** (22 mg, 96% mass recovery, 59% D by FI HRMS analysis), as a ~ 1:1 mixture of inseparable diastereomers: R_f 0.38 (petroleum ether/Et_2O 9:1); IR (neat/cm^{-1}) 2959 br, 2928 br, 1478 s, 1465 s, 1435 s, 1390 m, 1365 m, 1274 s, 1244 w, 1140 s, 1013 w, 993 w, 841 w, 735 w; ^1H NMR (400 MHz, $CDCl_3$) (3.2:1 rotamer mixture by analysis of NCH signals in the region 4.45−4.25) δ 4.32−4.25 (4.45−4.39) (m, 1H, NCH), 4.02−3.86 (m, 2H, NCH_2), 2.38−2.21 (m, 1H, NCH_2CHH'), 1.86−1.78 (m, 1H, NCH_2CHH'), 1.74−1.64 (1.96−1.87) (m, 2H, $CH_2(CH_2)_2CH_3$), 1.64 (1.63) (s, 9H, $C(CH_3)_3$), 1.39−1.23 (m, 4H, $CH_2CH_2CH_3$), 0.92 (t, J = 7.1 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamer mixture) δ 185.3 (185.1) (C═S), 84.7 (84.4) ($C(CH_3)_3$), 64.0 (65.1) (NCH), 49.4 (49.2) (NCH_2), 49.1 (T, J = 22.9 Hz, NCHD), 33.4 (32.2) ($CH_2(CH_2)_2CH_3$), 28.5 ($C(CH_3)_3$), 26.3 (26.1) ($CH_2CH_2CH_3$), 22.5 (22.6) (CH_2CH_3), 20.4 (21.0) (NCH_2CH_2), 14.0 (14.1) (CH_2CH_3); HRMS (FI^+) calcd for $C_{12}DH_{22}NOS$ 230.1563 $[M]^+$, found 230.1564.

*O-tert-Butyl 2-Butyl-4-methylazetidine-1-carbothioate (**17**).* *O-tert*-Butyl 2-butylazetidine-1-carbothioate (**14**)[9] (54 mg, 0.24 mmol) and MeI (44 μL, 0.71 mmol) were used following general procedure C with a lithiation time of 30 min. Purification of the resulting very pale yellow oil by column chromatography (SiO_2, 0−2% Et_2O/petroleum ether) gave a colorless oil, *N*-Botc-2,4-disubstituted azetidine **17** (26 mg, 46%, 68% brsm), as a ~ 1:1 mixture of inseparable diastereomers: R_f 0.47 (petroleum ether/Et_2O 9:1); IR (neat/cm^{-1}) 2960 w, 2928 w, 1467 s, 1433 s, 1390 w, 1365 w, 1224 s, 1143 s, 1001 w, 959 w, 842 w; ^1H NMR (500 MHz, $CDCl_3$) (rotamer mixture) δ 4.48−4.12 (m, 2H, HCNCH), 2.50−1.58 (m, 4H, NCHC*H*$_2$ and C*H*$_2(CH_2)_2CH_3$), 1.65 (1.64) (s, 9H, $C(CH_3)_3$), 1.57 (1.55) (d, J = 6.3 Hz, 1.5H, NCHC*H*$_3$), 1.48−1.20 (m, 4H, $CH_3(CH_2)_2$), 1.40 (1.41) (d, J = 6.3 Hz, 1.5H, NCHC*H*$_3$), 0.92 (0.90) (t, J = 6.9 Hz (J = 7.3 Hz), 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamer mixture) δ 184.11 (186.8) (C═S), 184.07 (186.7) (C═S), 84.5 (84.6) ($C(CH_3)_3$), 84.4 ($C(CH_3)_3$), 62.2 (62.9) (NCH), 61.6 (62.8) (NCH), 58.2 (58.9) (NCH), 57.8 (58.5) (NCH), 32.5 (35.3) ($NCHCH_2$), 31.1 (33.9) ($NCHCH_2$), 29.3 (29.44) ($NCHCH_2$), 29.0 (29.39) ($NCHCH_2$), 28.62 (28.55) ($C(CH_3)_3$), 26.0 (27.0) ($CH_2CH_2CH_3$), 25.7 (26.5) ($CH_2CH_2CH_3$), 22.6 (22.5) (CH_2CH_3), 20.4 (21.7) ($NCHCH_3$), 19.1 (20.9) ($NCHCH_3$), 14.1 (14.0) (CH_2CH_3); HRMS (FI^+) calcd for $C_{13}H_{25}NOS$ 243.1657 $[M]^+$, found 243.1667.

1-(Azetidin-1-yl)-2,2-dimethylpropan-1-one (18). *N*-Pivaloylazetidine **18** was prepared according to the literature procedure:[8a] ^1H NMR (500 MHz, toluene-d_8) δ 3.72 (t, J = 7.4 Hz, 4H, NCH_2), 1.56−1.50 (m, 2H, CH_2), 1.09 (s, 9H, $C(CH_3)_3$). All other data were consistent with the literature.[8a]

***tert*-Butyl Azetidine-1-carboxylate (19).** *N*-Boc-azetidine **19** was prepared according to the literature procedure:[9] ^1H NMR (500 MHz, toluene-d_8) δ 3.63 (t, J = 7.4 Hz, 4H, NCH_2), 1.50 (quin, J = 7.6 Hz, 2H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$). All other data were consistent with the literature.[9]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01804.

^1H and ^{13}C NMR spectra and computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tim.claridge@chem.ox.ac.uk (NMR studies).
*E-mail: robert.paton@chem.ox.ac.uk (computational studies).
*E-mail: david.hodgson@chem.ox.ac.uk (synthetic studies).

Present Address

[§]Novartis Institutes for BioMedical Research, 250 Massachusetts Avenue, Cambridge, MA 02139.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC for a studentship (to K.E.J.) and the EPSRC and Novartis for an Organic Synthesis Studentship (to C.L.M.). We also acknowledge the use of the EPSRC UK

DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846

National Service for Computational Chemistry Software at Imperial College (CHEM773) and thank Prof. P. Budzelaar (University of Manitoba) for providing the gNMR program.

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DOI: 10.1021/acs.joc.5b01804
J. Org. Chem. 2015, 80, 9838−9846