JOC The Journal of Organic Chemistry

Article

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α-Lithiation–Electrophile Trapping of *N*-Thiopivaloylazetidin-3-ol: Stereoselective Synthesis of 2-Substituted 3-Hydroxyazetidines

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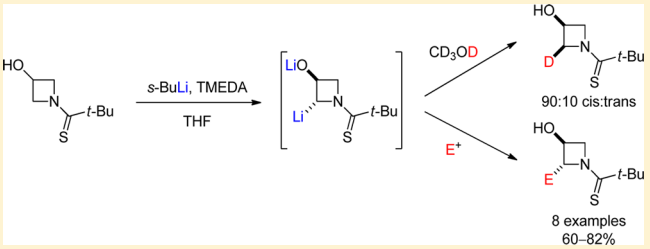
Supporting Information

ABSTRACT: α-Lithiation of *N*-thiopivaloylazetidin-3-ol and subsequent electrophile trapping provides access to a range of 2-substituted 3-hydroxyazetidines with generally good *trans*-diastereoselectivity, aside from deuteration, which gives the *cis*-diastereoisomer. Deuterium labeling studies indicate that the initial α-deprotonation occurs preferentially, but not exclusively, in a *trans*-selective manner. These studies also suggest that the stereochemical outcome of the electrophile trapping depends on the electrophile used but is independent of which α-proton (*cis* or *trans* to the hydroxyl group) is initially removed.



INTRODUCTION

Azetidines have received significantly less attention from the synthesis community in comparison with the larger and smaller azacycles.[1] However, azetidines are being increasingly incorporated into drug candidates[2] and are also finding utility as ligands in metal-catalyzed transformations.[3] In particular, the 3-hydroxy- or 3-alkoxyazetidine motif is present in a number of drug leads[4] and in natural products[5] (Figure 1).

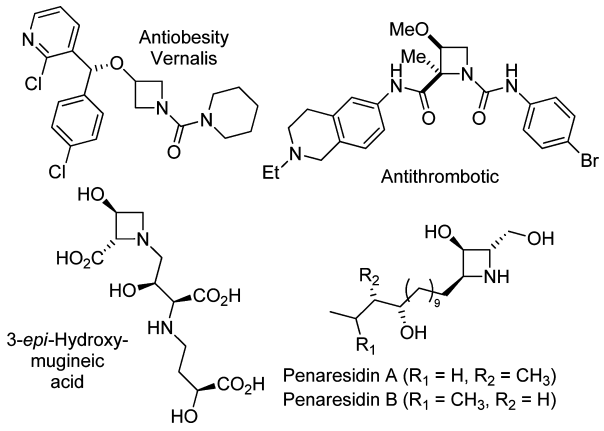
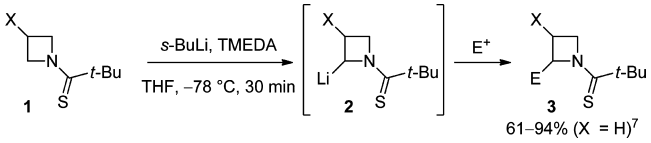


Figure 1. Examples of 3-oxygenated azetidine-containing drug leads[4] and natural products.[5]

In most strategies to substituted azetidines, the substituents are required to be present on a precursor or precursors, prior to ring formation.[1,6] We recently reported a method for α-electrophile incorporation on azetidine **1** (Scheme 1, X = H), in which the rarely studied *N*-thiopivaloyl group plays a crucial role.[7] The ready availability of the 3-hydroxyazetidine system (from epichlorohydrin and benzhydrylamine)[8] and its value in medicinal chemistry programs prompted the present investigations of the 3-oxygenated system **1** (Scheme 1, X = OR). Despite the potential issues of β-elimination from the α-lithiated intermediate **2** and controlling diastereoselectivity in the electrophile trapping, this work has resulted in a promising entry to 2,3-disubstituted azetidines **3** (X = OR).

Scheme 1. α-Deprotonation and Electrophile Trapping of *N*-Thiopivaloylazetidine



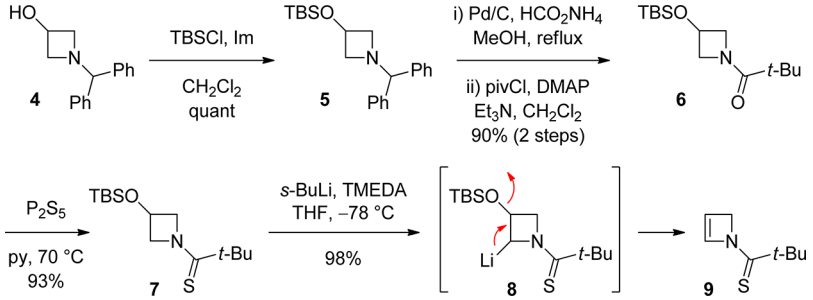
RESULTS AND DISCUSSION

We initially attempted lithiation–deuteration (as well as in situ silylation) of silyloxythioamide **7** (Scheme 2). Silyloxythioamide **7** was prepared in four steps from *N*-benzhydrylazetidin-3-ol (**4**), by silylation to give silyl ether **5** (quant), hydrogenolytic N-deprotection and N-pivaloylation to give silyloxyamide **6** (90% over two steps), and finally, amide thionation using P_2S_5 (93%). However, only starting thioamide **7** and/or azetine **9** (up to 98% yield) were obtained from the lithiation experiments. Azetine **9** is likely formed by rapid β-elimination of silyloxide from the transient α-lithiated intermediate **8**.[9]

With the aim of avoiding the undesired elimination pathway, we examined C,O-dilithiation of the unprotected azetidinol **12**.[10] This azetidinol **12** could be conveniently prepared in two steps from commercially available azetidin-3-ol hydrochloride

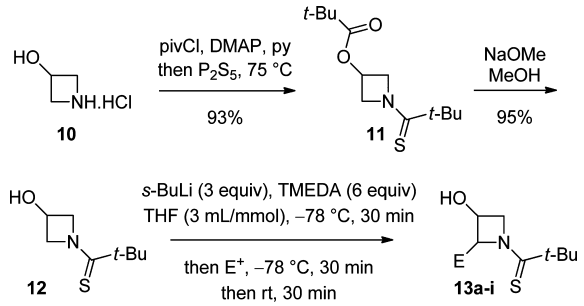
Received: November 19, 2012
Published: January 10, 2013

Scheme 2. Synthesis and Lithiation–Elimination of Silyloxythioamide 7



(**10**) (Scheme 3), by diacylation and amide thionation (93%), followed by de-esterification (95%) of the resulting thioamide ester **11**.

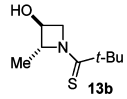
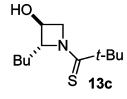
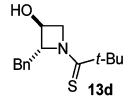
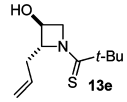
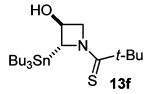
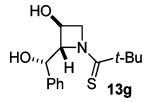
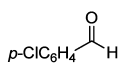
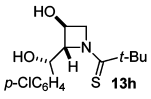
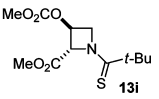
Scheme 3. Synthesis and Lithiation of Azetidinol 12



In the event, azetidinol **12** underwent partial lithiation–deuteration (92% recovery, 48% D, 90:10 dr) under the conditions originally used with azetidine **1** (X = H) but using twice the quantity of *s*-BuLi (2.4 equiv) to take account of the free hydroxyl. Further experimentation in THF established that complete deuterium incorporation to give **13a** (E = D) could be obtained by increasing the concentration (from 0.1 to 0.3 M), with the optimal yield (91%, 90:10 dr) being obtained using the conditions indicated in Scheme 3. Lithiation above −78 °C led to reduced dr values (73:26 at −46 °C), whereas no significant improvement was observed at −98 °C. Using no, or decreased equivalents, of TMEDA did give product but in slightly suppressed yields. Experiments carried out in Et_2O did not give higher than 33% deuterium incorporation, with poor solubility of the deprotonated species likely being a contributory factor. Application of the optimized conditions in THF to a range of other electrophiles gave the results shown in Table 1.

Alkylation (entries 1–4), including benzylation and allylation (entries 3 and 4), as well stannylation (entry 5), and reaction with aromatic aldehydes (entries 6 and 7) and with Mander's reagent (entry 8) all proceeded to give the corresponding 2,3-disubstituted azetidine **13** in good yield. Aside from methylation (entry 1),[11] high *trans*-2,3-diastereoselectivity was observed with the electrophiles in Table 1. With azetidine **1** (X = H), benzaldehyde and *para*-chlorobenzaldehyde had previously given the adduct alcohols as single diastereomers;[7] for azetidinol **12**, these prochiral electrophiles led to the same relative stereochemistry between C-2 and the side-chain carbinol but at a reduced level (entries 6 and 7). The reaction with methyl cyanoformate gave *C*- and *O*-methoxycarbonylated azetidine **13i** (entry 8), which provides potential access to azetidine amino acids and mugineic acid-type natural products

Table 1. Scope of Electrophile Incorporation into Azetidinol 12

entry	electrophile	2,3-disubstituted azetidine **13**	yield (%)
1	MeI	 **13b**	72[a]
2	BuI	 **13c**	68
3	BnBr	 **13d**	74
4		 **13e**	60
5	Bu_3SnCl	 **13f**	82
6		 **13g**	72[b]
7		 **13h**	81[b]
8		 **13i**	68[a]

[a]Ratio of *trans*/*cis* 69:31 (entry 1), 93:7 (entry 8); major diastereoisomer shown. [b]Ratio of 75:25 (entry 6) and 57:43 (entry 7) mixture of epimers at side-chain carbinol; major diastereoisomer shown.

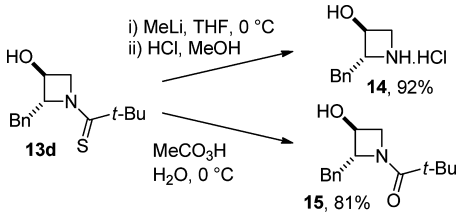
(Figure 1). The above stereochemical assignments are based on X-ray crystallographic analysis of the minor epimer *epi*-**13g** (epimeric to **13g** at the side-chain benzylic position) derived from benzaldehyde[12] and proton coupling constant analysis.[13] The vicinal coupling constant between the ring protons at C-2 and C-3 was 3.3 Hz for both **13g** and *epi*-**13g** and was similar (2–4 Hz) for all other adducts in Table 1.[14] In contrast, ^3J for

dx.doi.org/10.1021/jo3025225 | J. Org. Chem. 2013, 78, 1098–1106

the corresponding minor *cis*-methylated diastereoisomer of **13b** was 6.6 Hz.

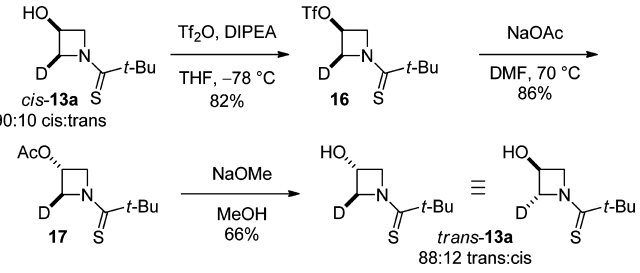
Effective deprotection of an α-substituted azetidinol **13** can be achieved using MeLi in THF with TMEDA at 0 °C (92% from **13d**, isolated as the hydrochloride salt **14**, Scheme 4). Conversion to the corresponding pivalamide **15**, in 81% yield from **13d**, was facilitated using $MeCO_3H$.

Scheme 4. Deprotection and Thioamide to Amide Conversion



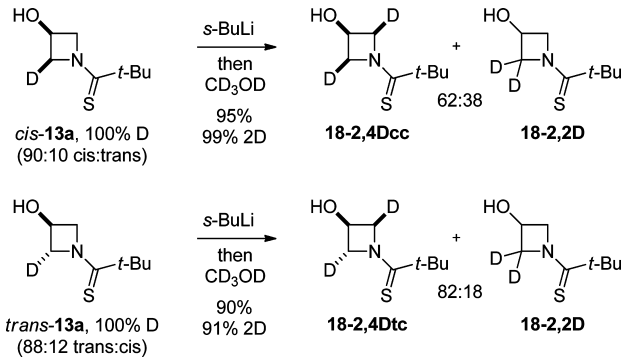
In contrast to the results shown in Table 1, deuterium trapping of lithiated azetidinol **12** occurs predominantly *cis* to the hydroxyl group (*cis*-**13a**, 90:10 *cis*/*trans*). This *cis* configuration was assigned from ^{1}H NMR analysis.[13] On deuteration, the appearance of the multiplet due to H-3 at the carbinol carbon changed from a triplet of triplets (^3J = 6.6 and 3.9 Hz) for **12** to a triplet of doublets (^3J = 6.6 and 3.9 Hz) for *cis*-**13a**, indicating the loss of a 3.9 Hz coupling, corresponding to loss of a proton *cis* to the alcohol. These observations prompted an investigation into the stereoselectivity of the lithiation and electrophile trapping steps,[15] using *cis*-**13a** and the inverted deuterium adduct *trans*-**13a**. The latter was synthesized by inversion of the alcohol in *cis*-**13a** through acetate displacement of the derived triflate **16** to give acetate **17**, followed by deacetylation (Scheme 5). In contrast to *cis*-**13a**, H-3 for the inverted deuterium adduct *trans*-**13a** appeared as a doublet of triplets (^3J = 6.6 and 3.9 Hz).

Scheme 5. Synthesis of *trans*-13a



The preference for proton removal (*cis* or *trans* to OLi under the reaction conditions) was examined by lithiation−deuteration of *cis*-**13a** and of *trans*-**13a**, which gave dideuterated adducts **18** (Scheme 6). 2,4-Dideuterated adduct is present in a greater proportion from *trans*-**13a** (2,4-:2,2-, 82:18) than from *cis*-**13a** (2,4-:2,2-, 62:38), indicating a preference for *trans*-deprotonation, which in the case of *trans*-**13a** is blocked at C-2 by the presence of the *trans*-deuterium (primary kinetic isotope effect). While less preferable to *trans*-deprotonation, *cis*-deprotonation does occur competitively, as evidenced by the formation of the 2,2-dideuterated adduct **18-2,2D** from *trans*-**13a** and the unequal ratio of dideuterated adducts from *cis*-**13a** (assuming no significant secondary kinetic isotope effect). The presence of ∼10% of *trans*-**13a** in *cis*-**13a** and visa versa (which

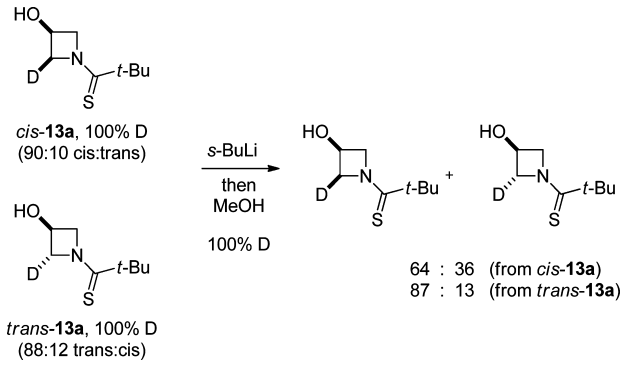
Scheme 6. Lithiation−Deuteration of *cis*-13a and of *trans*-13a



should lead to small amounts **18-2,4Dtc** and **18-2,4Dcc**, respectively—although not detectable/analyzable by NMR) does not negate these conclusions.

Lithiation−protonation of *cis*-**13a** and of *trans*-**13a** resulted in a *cis*/*trans* dr change from 90:10 to 64:36 (quant) and no change in dr (86% yield), respectively (Scheme 7).[13] These

Scheme 7. Lithiation−Protonation of *cis*-13a and of *trans*-13a



results can be rationalized as follows. The earlier dideuteration results with *cis*-**13a** and *trans*-**13a** (Scheme 6) indicate that the regioselectivity of the deprotonation between the 4- and 2-positions is ∼6:4 and 8:2, respectively, in favor of the 4-position. On lithiation−protonation of *cis*-**13a** (Scheme 7), the 4-lithiated intermediate (comprising ∼60% of the total lithiated azetidinol) will regenerate *cis*-**13a**, whereas the 2-lithiated species (∼40%) will give *trans*-**13a**. However, for lithiation−protonation of *trans*-**13a**, both the 4-lithiated *and* the 2-lithiated species regenerate *trans*-**13a**. These results therefore suggest that there is a strong bias for *cis*-protonation (deuteration), regardless of whether a *cis* or *trans* proton is originally removed.

Lithiation−benzylation of *cis*-**13a** and of *trans*-**13a** both result in a mixture of the two possible regioisomers: the *cis*- and *trans*-2-deuterated 4-benzylated derivatives (**19-2D$_c$-4Bn$_t$** and **19-2D$_t$-4Bn$_t$**) and the 2,2-derivative (**19-2D$_c$-2Bn$_t$**) (Scheme 8). The *cis*- and *trans*-2,4-derivatives (where *cis* and *trans* refer to stereochemistry relative to the alcohol) likely derive directly from 4-lithiation of the major and minor diastereoisomeric azetidinols which comprise the starting material, as the ratios match. Both stereoisomers can be observed in these cases, as the position of the deuterium can now be established relative to the newly installed benzyl group. 2-Lithiation−benzylation from either *cis*-**13a** or *trans*-**13a** gave only the *trans*-2-

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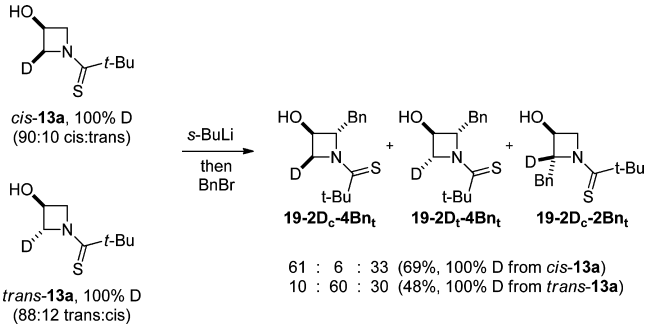
Scheme 8. Lithiation−Benzylation of *cis*-13a and of *trans*-13a



benzylated adduct **19-2D$_c$-2Bn$_t$**.[16] These observations indicate that there is a strong bias for electrophile trapping (apart from protonation/deuteration) to occur *trans* to the C-3 lithium alkoxide, regardless of whether a *cis* or *trans* proton is initially removed at C-2. However, further conclusions concerning configurational (in)stability of the intermediate organolithiums and whether the electrophile trapping step occurs with retention/inversion/SET pathways cannot be made from the results obtained.

CONCLUSIONS

In summary, readily available *N*-thiopivaloylazetidin-3-ol (**12**) has been shown to undergo α-lithiation−electrophile trapping with a range of electrophiles, providing 2-substituted 2-hydroxyazetidines **13**. Deuterium labeling studies indicate that the α-deprotonation step is preferentially, but not exclusively, *trans*-stereoselective. Nevertheless, high *trans*-diastereoselectivity is observed on incorporation of most electrophiles. A notable exception is protonation, where the alkoxide may be involved in directing the protonation *cis* to itself.[17] Our work indicates that the stereochemical outcome of the lithiated azetidinol trapping depends on the electrophile used but is independent of which α-proton (*cis* or *trans* to the hydroxyl group) is initially removed. These studies demonstrate that electrophile incorporation with high levels of diastereocontrol is possible on a simple azetidine and suggest that further opportunities exist for azetidine diversity generation using this strategy.

EXPERIMENTAL SECTION

3-((*tert*-Butyldimethylsilyl)oxy)-1-(diphenylmethyl)azetidine (5). To a stirred solution of *N*-benzhydrylazetidin-3-ol (**4**) (3.60 g, 15.0 mmol) and TBSCl (2.73 g, 18.1 mmol) in CH_2Cl_2 (30 mL) at rt was added imidazole (1.23 g, 18.1 mmol). After 30 min, the reaction mixture was filtered, and the filter cake washed with CH_2Cl_2 (10 mL). The filtrate was concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/Et_2O 1:0→9:1) gave silyl ether **5**[18] as an off-white solid (5.30 g, quant): R_f 0.83 (pet ether/EtOAc 3:2); mp 45−47 °C; IR (neat/cm^{-1}) 2929 w, 2854 w, 2832 w, 1451 w, 1307 w, 1204 m, 1204 m, 1182 m, 1160 w, 880 m, 836 m, 780 m, 703 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.18 (10H, m, Ar), 4.47 (1H, quint, J = 6.1 Hz, CHO), 4.37 (1H, s, C$\underline{H}$Ph$_2$), 3.55 (1H, dd, J = 6.1, 2.0 Hz, NC$\underline{H}$H), 3.53 (1H, dd, J = 6.1, 2.0 Hz, NC$\underline{H}$H), 2.84 (1H, dd, J = 6.3, 2.0 Hz, NCH$\underline{H}$), 2.82 (1H, dd, J = 6.3, 2.0 Hz, NCH$\underline{H}$), 0.87 (9H, s, Si(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), 0.03 (6H, s, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3 (Ar), 128.4 (Ar), 127.4 (Ar), 127.0 (Ar), 78.6 (N$\underline{C}$HPh$_2$), 63.8 (NCH$_2$), 61.8 (CHO), 25.8 (Si(CH$_3$)$_2$C($\underline{C}$H$_3$)$_3$), 18.0 (Si(CH$_3$)$_2\underline{C}$(CH$_3$)$_3$), −5.0 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); LRMS (ESI$^+$) 354.20 ([M + H]$^+$, 80%); HRMS (ESI$^+$) calcd for $C_{22}H_{32}NOSi$ 354.2248, found 354.2236.

1-(3-((*tert*-Butyldimethylsilyl)oxy)azetidin-1-yl)-2,2-dimethylpropan-1-one (6). To a stirred solution of silyl ether **5** (5.30 g, 15.0 mmol) in MeOH (100 mL) at rt were added ammonium formate (4.73 g, 75.0 mmol) and 10 wt % Pd/C (530 mg) under nitrogen. The reaction mixture was heated to reflux, and after 2 h, upon cooling to rt, the reaction mixture was filtered through a pad of Celite, then concentrated to dryness under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (75 mL). To the resulting solution were added DMAP (670 mg, 5.5 mmol) and Et_3N (4.2 mL, 30.1 mmol). The reaction mixture was cooled to 0 °C, and pivCl (2.2 mL, 17.9 mmol) was added dropwise over 5 min. The reaction mixture was warmed slowly to rt and stirred overnight. After quenching with aq HCl (1 M, 75 mL) the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (75 mL) then brine (75 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 19:1→4:1) gave silyloxyamide **6** as a white solid (3.65 g, 90%): R_f 0.36 (pet ether/Et_2O 3:2); mp 32−34 °C; IR (neat/cm^{-1}) 2956 m, 2931 m, 2858 w, 1628 s, 1415 m, 1131 m, 988 m, 836 m, 777 m; ^{1}H NMR (500 MHz, T = 363 K, toluene-d_8) δ 4.21 (1H, m, CHO), 4.05 (2H, dd, J = 9.1, 6.9 Hz, NC$\underline{H}$H), 3.84 (2H, dd, J = 9.1, 4.1 Hz, NCH$\underline{H}$), 1.08 (9H, s, C(O)C(CH$_3$)$_3$), 0.84 (9H, s, Si(CH$_3$)$_2$C(C$\underline{H}_3$)$_3$), −0.07 (6H, s, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$); ^{13}C NMR (125 MHz, T = 363 K, toluene-d_8) δ 177.1 (C═O), 62.7 (CHO), 61.4 (N−CH$_2$), 38.9 (C(O)$\underline{C}$(CH$_3$)$_3$), 27.7 (C($\underline{C}$H$_3$)$_3$), 26.0 (C($\underline{C}$H$_3$)$_3$), 18.2 (Si(CH$_3$)$_2\underline{C}$-(CH$_3$)$_3$), −4.8 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); LRMS (ESI$^+$) 272.2 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{14}H_{30}NO_2Si$ 272.2040, found 272.2039.

1-(3-(*tert*-Butyldimethylsilyloxy)azetidin-1-yl)-2,2-dimethylpropane-1-thione (7). To a stirred solution of silyloxyamide **6** (3.65 g, 13.4 mmol) in pyridine (40 mL) at rt was added P_2S_5 (3.70 g, 16.6 mmol). The reaction mixture was heated to 75 °C for 2 h, then after cooling to rt was concentrated under reduced pressure to ∼20 mL. The partially concentrated reaction mixture was poured onto aq HCl (1 M, 100 mL) and stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with aq HCl (1 M, 100 mL), H_2O (100 mL), then brine (100 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/Et_2O 1:0→9:1) gave silyloxythioamide **7** as a white solid (3.60 g, 93%): R_f 0.57 (pet ether/Et_2O 9:1); mp 56−58 °C; IR (neat/cm^{-1}) 2960 m, 2929 m, 2858 m, 1487 m, 1470 m, 1128 s, 841 s, 775 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, ddd, J = 10.6, 6.6, 2.0, Hz, NC$\underline{H}$H), 4.58 (1H, tt, J = 6.6, 4.3 Hz, OC$\underline{H}$), 4.48 (1H, ddd, J = 12.4, 6.6, 2.0 Hz, NC$\underline{H}$H), 4.24 (1H, ddd, J = 10.6, 4.3, 2.0 Hz, NCH$\underline{H}$), 4.07 (1H, ddd, J = 12.4, 4.3, 2.0 Hz, NCH$\underline{H}$), 1.34 (9H, s, C(S)C(C$\underline{H}_3$)$_3$), 0.89 (9H, s, Si(CH$_3$)$_2$C-(C$\underline{H}_3$)$_3$), 0.07 (3H, s, Si(C$\underline{H}_3$)$_2$C(CH$_3$)$_3$), 0.07 (3H, s, Si(C$\underline{H}_3$)$_2$C-(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C═S), 66.2 (NCH$_2$), 66.0 (NCH$_2$), 60.3 (CHO), 43.2 (C(S)$\underline{C}$(CH$_3$)$_3$), 29.7 (C($\underline{C}$H$_3$)$_3$), 25.6 (C($\underline{C}$H$_3$)$_3$), 17.9 (Si(CH$_3$)$_2\underline{C}$(CH$_3$)$_3$), −5.0 (Si-($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$), −5.1 (Si($\underline{C}$H$_3$)$_2$C(CH$_3$)$_3$); LRMS (FI$^+$) 287.17 ([M]$^+$, 100%); HRMS (FI$^+$) calcd for $C_{14}H_{29}NOSSi$ 287.1739, found 287.1737.

1-(2-Azetinyl)-2,2-dimethylpropane-1-thione (9). To a stirred solution of silyloxythioamide **7** (100 mg, 0.35 mmol) in THF (1 mL) at −78 °C was added TMEDA (315 μL, 2.10 mmol). *s*-BuLi (777 μL, 1.35 M in cyclohexane/hexane (92/8), 1.05 mmol) was added dropwise to the reaction mixture over 5 min, resulting in a characteristic deep yellow color. After 30 min, MeOH (71 μL, 1.75 mmol) was added, and the reaction mixture was stirred for 10 min. The cooling bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/Et_2O 9:1) gave azetine **9** as a yellow syrup (53 mg, 98%): R_f 0.30 (pet ether/Et_2O 9:1); IR (neat/cm^{-1}) 2968 w, 1456 s, 1364 w, 1137 m, 935 m, 689 m; ^{1}H NMR (400 MHz, $CDCl_3$, 3:1 mixture of rotamers) (major rotamer) δ 6.98 (1H, s, NCH), 6.04 (1H, s, NCH═C$\underline{H}$), 4.67 (2H, s, NCH$_2$), 1.38 (9H, s, C(CH$_3$)$_3$); (minor rotamer) δ

dx.doi.org/10.1021/jo3025225 | J. Org. Chem. 2013, 78, 1098−1106

7.35 (1H, s, NCH), 6.14 (1H, s, NCH=CH), 4.86 (2H, s, NCH_2), 1.42 (3H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) (major rotamer) δ 203.8 (C=S), 139.4 (NCH), 118.0 (NCH=CH), 62.0 (NCH_2), 43.0 ($C(CH_3)_3$), 30.3 ($C(CH_3)_3$); (minor rotamer) δ 203.8 (C=S), 141.7 (NCH), 118.7 (NCH=CH), 63.9 (NCH_2), 43.0 ($C(CH_3)_3$), 31.0 ($C(CH_3)_3$); LRMS (FI^+) 155.08 ($[M]^+$,100%); HRMS (FI^+) calcd for $C_8H_{13}NS$ 155.0769, found 155.0767.

1-(2,2-Dimethylpropanethioyl)azetidin-3-yl pivalate (11). A suspension of azetidin-3-ol hydrochloride (**10**) (8.0 g, 73 mmol) in py (80 mL) was heated to 50 °C for 5 min, then cooled to rt. DMAP (1.8 g, 15 mmol) and pivCl (22 mL, 179 mmol) were added, and after 1 h, P_2S_5 (19 g, 85 mmol) and py (50 mL) were added and the reaction mixture was heated to 75 °C. After 1 h, the reaction mixture was cooled, concentrated to half volume under reduced pressure, diluted with EtOAc (200 mL), and washed with aq HCl (2 M, 500 mL). The organic layer was washed successively with H_2O (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, heptane/EtOAc 1:0→4:1) gave thioamide ester **11** as a colorless syrup which solidified on standing (17.4 g, 93%): R_f 0.45 (heptane/EtOAc 4:1); mp 50−52 °C; IR (neat/cm^{-1}) 2965 w, 2872 w, 1781 s, 1484 m, 1465 m, 1321 m, 1139 s, 1004 w, 890 m; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (1H, tt, J = 6.8, 4.2 Hz, CHO), 4.80 (1H, ddd, J = 11.6, 6.8, 2.1 Hz, NCHH), 4.54 (1H, ddd, J = 13.3, 6.8, 2.1 Hz, NCHH), 4.27 (1H, ddd, J = 11.6, 4.2, 2.1 Hz, NCHH), 4.19 (1H, ddd, J = 13.3, 4.2, 2.1 Hz, NCHH), 1.33 (9H, s, $C(CH_3)_3$), 1.21 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6 (C=S), 178.0 (C(O)), 63.3 (NCH_2), 62.0 (CHO), 61.9 (NCH_2), 43.2 ($C(S)C(CH_3)_3$), 38.5 ($C(O)C(CH_3)_3$), 29.7 ($C(S)C(CH_3)_3$), 26.9 ($C(O)C(CH_3)_3$); LRMS (ESI^+) 280.12 ($[M + Na]^+$ 100%); HRMS (ESI^+) calcd for $C_{13}H_{23}NNaO_2S$ 280.1342, found 280.1339.

1-(3-Hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (12). To a solution of thioamide ester **11** (15.0 g, 58 mmol) in MeOH (20 mL) was added NaOMe (26 mL, 25 wt % in MeOH, 117 mmol). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure and the crude reaction mixture purified (Si gel, heptane/EtOAc 1:0→2:3) to give azetidinol **12** as a colorless syrup which solidified on standing (9.6 g, 95%): R_f 0.27 (pet ether/EtOAc 3:2); mp 54−56 °C; IR (neat/cm^{-1}) 3363 br, 2968 w, 1471 s, 1447 s, 1137 m, 1007 m, 730 s; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, ddd, J = 11.0, 6.6, 2.0 Hz, NCHH), 4.63 (1H, tt, J = 6.6, 3.9 Hz, CHOH), 4.47 (1H, ddd, J = 13.1, 6.6, 2.3 Hz, NCHH), 4.31 (1H, ddd, J = 11.0, 3.9, 2.3 Hz, NCHH), 4.09 (1H, ddd, J = 13.1, 3.9, 2.0 Hz, NCHH), 3.26 (1H, br, OH), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 ($C(S)C(CH_3)_3$), 65.8 (NCH_2), 65.5 (NCH_2), 59.9 (CHOH), 43.2 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (FI^+) 173.09 ($[M]^+$, 100%); HRMS (FI^+) calcd for $C_8H_{15}NOS$ 173.0874, found 173.0879.

General Procedure A: α-Deprotonation/Electrophile Trapping of Azetidinol 12. To a stirred solution of azetidinol **12** (100 mg, 0.58 mmol) in THF (2 mL) at −78 °C under argon was added TMEDA (519 μL, 3.46 mmol). *s*-BuLi (1.24 mL 1.40 M in cyclohexane/hexane (92:8), 1.73 mmol) was added dropwise to the reaction mixture over 5 min, resulting in a characteristic deep yellow color. After 30 min, the electrophile was added and the reaction mixture stirred for 30 min. The cooling bath was removed, and the reaction mixture was stirred for another 30 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure.

1-(2-Deutero-3-(hydroxy)-azetidin-1-yl)-2,2-dimethylpropane-1-thione (*cis*-13a). CD_3OD (70 μL, 1.7 mmol) was used following General Procedure A. Purification (Si gel, pet ether/EtOAc 3:2) gave the deuterated azetidinol **13a** as a colorless syrup which solidified on standing (92 mg, 91%, 100% D, 90:10 *cis*/*trans*,[13] dr determined by integration at δ_H 4.67 + 4.42 and 4.28 + 4.04): R_f 0.27 (pet ether/EtOAc 3:2); mp 54−56 °C; IR (neat/cm^{-1}) 3361 br, 2966 m, 1467 s, 1395 w, 1134 s, 1006 m; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (0.95H, dd, J = 11.0, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.59 (1H, td, J = 6.6, 3.9 Hz, CHOH), 4.42 (0.95H, dd, J = 13.1, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.28 (0.53H, ddd, J = 11.0, 3.9, 2.3 Hz, $NCH_{cis}H_{trans}$), 4.04 (0.57H, ddd, J = 13.1, 3.9, 2.3 Hz, $NCH_{cis}H_{trans}$), 3.75 (1H, br, OH), 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C=S), 65.8 (NCH_2), 65.5 (t, J = 23 Hz, NCHD), 65.4 (NCH_2), 65.1 (t, J = 23 Hz, NCHD), 59.6 (CHOH), 59.6 (t, J = 7 Hz, CHOH), 43.1 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$); LRMS (ESI^+) 175.11 ($[M + H]^+$, 85%); HRMS (ESI^+) calcd for $C_8H_{15}DNOS$ 175.1010, found 175.1011.

1-(3-Hydroxy-2-methyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (13b). MeI (180 μL, 2.9 mmol) was used following General Procedure A, but on half the scale. Purification (Si gel, pet ether/EtOAc 4:1) gave methylated azetidinol **13b** as a pale yellow syrup (39 mg, 72%, 69:31 *trans*/*cis*,[13] dr determined by integration at δ_H 1.32 and 1.30): R_f 0.38 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3364 br, 2965 w, 2929 w, 1461 s, 1434 s, 1364 w, 1135 m; LRMS (ESI^+) 188.12 ($[M + H]^+$, 40%); HRMS (ESI^+) calcd for $C_9H_{18}NOS$ 188.1104, found 188.1105. **Major diastereoisomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, ddd, J = 11.4, 6.1, 2.4 Hz, $NCH_{cis}H_{trans}$), 4.59 (1H, qdd, J = 6.6, 3.0, 2.4 Hz, NCH), 4.23 (1H, dd, J = 11.4, 3.0 Hz, $NCH_{cis}H_{trans}$), 4.14 (1H, dt, J = 6.1, 3.0 Hz, CHOH), 3.18 (1H, br, OH), 1.56 (3H, d, J = 6.6 Hz, CH_3), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2 (C=S), 74.0 (NCH), 67.9 (CHOH), 64.6 (NCH_2), 43.5 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$), 16.0 ($CHCH_3$). **Minor diastereoisomer**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (1H, qd, J = 6.6, 6.6 Hz, NCH), 4.74 (1H, m, CHOH), 4.67 (1H, ddd, J = 10.9, 7.3, 1.0 Hz, $NCH_{cis}H_{trans}$), 4.33 (1H, ddd, J = 10.9, 5.3, 2.0 Hz, $NCH_{cis}H_{trans}$), 2.82 (1H, br, OH), 1.55 (3H, d, J = 6.6 Hz, CH_3), 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3 (C=S), 70.6 (NCH), 64.6 (NCH_2), 61.7 (CHOH), 43.3 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$), 10.3 ($CHCH_3$).

1-(3-Hydroxy-2-butyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (13c). BuI (986 μL, 8.66 mmol) was used following General Procedure A, but on five times the scale. Purification (Si gel, pet ether/EtOAc 19:1→4:1) gave butylated azetidinol **13c** as a pale yellow syrup (451 mg, 68%): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3372 br, 2958 w, 2923 m, 2854 m, 1461 s, 1435 m, 1363 w, 1134 m, 737 m; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, ddd, J = 12.6, 7.5, 1.8 Hz, $NCH_{cis}H_{trans}$), 4.52 (1H, m, NCH), 4.24−4.19 (2H, m, CHOH and $NCH_{cis}H_{trans}$), 2.90 (1H, br s, OH), 2.41−2.33 (1H, m, $CHHCH_2CH_2CH_3$), 1.67 (1H, ddt, J = 14.7, 7.3, 7.1 Hz, $CHHCH_2CH_2CH_3$), 1.38−1.24 (4H, m, $CH_2CH_2CH_2CH_3$), 1.33 (9H, s, $C(CH_3)_3$), 0.91 (3H, t, J = 7.1 Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C=S), 78.0 (NCH), 66.6 (CHOH), 64.9 (NCH_2), 43.5 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 28.3 ($CH_2CH_2CH_2CH_3$), 25.9 ($CH_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_3$); LRMS (ESI^+) 230.17 ($[M + H]^+$, 55%); HRMS (ESI^+) calcd for $C_{12}H_{24}NOS$ 230.1573, found 230.1569.

1-(3-Hydroxy-2-benzyl-azetidin-1-yl)-2,2-dimethylpropane-1-thione (13d). BnBr (1.03 mL, 8.66 mmol) was used following General Procedure A, but on five times the scale. Purification (Si gel, heptane/EtOAc 9:1→8:2) gave benzylated azetidinol **13d** as a pale yellow syrup (559 mg, 74%): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3365 br, 2966 w, 2930 w, 1455 s, 1432 s, 1125 m, 995 m, 702 s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (5H, m, Ar), 4.83 (1H, dddd, J = 7.8, 3.3, 3.0, 2.0 Hz, NCH), 4.28 (1H, dt, J = 6.1, 3.0 Hz, CHOH), 4.22 (1H, ddd, J = 11.1, 6.1, 2.0 Hz, $NCH_{cis}H_{trans}$), 4.10 (1H, dd, J = 11.1, 3.0 Hz, $NCH_{cis}H_{trans}$), 3.46 (1H, dd, J = 13.9, 3.3 Hz, CHHPh), 3.36 (1H, dd, J = 13.9, 7.8 Hz, CHHPh), 1.86 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (C=S), 136.4 (Ar), 129.7 (Ar), 128.4 (Ar), 126.7 (Ar), 77.5 (NCH), 65.2 (CHOH), 64.7 (NCH_2), 43.6 ($C(CH_3)_3$), 33.8 (CH_2Ph), 29.6 ($C(CH_3)_3$); LRMS (ESI^+) 286.14 ($[M + Na]^+$, 100%); HRMS (ESI^+) calcd for $C_{15}H_{22}NOS$ 264.1417, found 264.1414.

1-(2-Allyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (13e). Allyl bromide (75 μL, 0.87 mmol) was used following General Procedure A, but on half the scale. Purification (Si gel, pet ether/EtOAc 9:1→1:1) gave allylated azetidinol **13e** as a yellow syrup (37 mg, 60%): R_f 0.23 (pet ether/EtOAc 4:1); IR (neat/cm^{-1}) 3369 br, 2966 w, 2872 w, 1460 s, 1395 w, 1135 m, 1001 s, 918 m, 796 w,

dx.doi.org/10.1021/jo3025225 | J. Org. Chem. 2013, 78, 1098−1106

732 w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, ddt, J = 17.2, 10.1, 7.1 Hz, CH_2CH=$CH_{cis}H_{trans}$), 5.18 (1H, d J = 17.2 Hz, CH_2CH=$CH_{cis}H_{trans}$), 5.16 (1H, d, J = 10.1 Hz, CH_2CH=$CH_{cis}H_{trans}$), 4.65–4.61 (2H, m, NCH and $NCH_{cis}H_{trans}$), 4.27 (1H, dt, J = 6.5, 3.0 Hz, CHOH), 4.22 (1H, dd, J = 11.0, 3.2 Hz, $NCH_{cis}H_{trans}$), 2.92 (1H, ddd, J = 14.5, 7.5, 2.5 Hz, $CHHCH$=CH_2), 2.76 (1H, ddd, J = 14.5, 7.5, 7.0 Hz, $CHHCH$=CH_2), 2.66 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (C=S), 131.9 (CH=CH_2), 119.0 (CH=CH_2), 76.4 (NCH), 65.4 (CHOH), 64.9 (NCH_2), 43.6 ($C(CH_3)_3$), 32.6 (CH_2CH=CH_2), 29.7 ($C(CH_3)_3$); LRMS (ESI$^+$) 214.13 ([M + H]$^+$, 85%); HRMS (ESI$^+$) calcd for $C_{11}H_{19}NNaOS$ 236.1080, found 236.1082.

1-(3-Hydroxy-2-(tributylstannyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (13f). Bu_3SnCl (2.3 mL, 8.48 mmol) was used following General Procedure A, but on five times the scale. Purification (Si gel, pet ether/EtOAc 39:1→4:1) gave stannylated azetidinol **13f** as a colorless syrup (1.1 g, 82%): R_f 0.33 (pet ether/EtOAc 9:1); IR (neat/cm^{-1}) 3361 br, 2923 w, 2854 w, 1465 s, 1364 w, 1124 w, 910 m, 732 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, ddd, J = 11.6, 5.8, 2.5 Hz, $NCH_{cis}H_{trans}$), 4.58 (1H, ddt, J = 6.3, 5.8, 3.3 Hz, CHOH), 4.40–4.38 (1H, m, NCH), 4.36 (1H, dd, J = 11.6, 3.3. Hz, $NCH_{cis}H_{trans}$), 2.30 (1H d, J = 6.3 Hz, CHOH), 1.65–1.42 (6H, m, $CH_2CH_2CH_2CH_3$), 1.35 (9H, s, $C(CH_3)_3$), 1.36–1.26 (6H, m, $CH_2CH_2CH_2CH_3$), 0.97–0.92 (6H, m, $CH_2CH_2CH_2CH_3$), 0.90 (9H, t, J = 7.3 Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5 (C=S), 71.6 (NCH), 66.0 (NCH_2), 64.9 (CHOH), 42.7 ($C(CH_3)_3$), 30.0 ($CH_2CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_3$), 27.5 ($C(CH_3)_3$), 13.7 ($CH_2CH_2CH_2CH_3$), 11.5 ($CH_2CH_2CH_2CH_3$); LRMS (ESI$^+$) 464.20 ([M + H]$^+$, 68%); HRMS (ESI$^+$) calcd for $C_{20}H_{41}NOSSn$ 464.2005, found 464.1991.

1-(3-Hydroxy-2-(hydroxy(phenyl)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (13g). Benzaldehyde (352 μL, 3.46 mmol) was used following General Procedure A, but on twice the scale. By TLC, both diastereoisomers appeared to have the same R_f, with residual starting azetidinol **12** also falling at the same R_f. Purification (Si gel, heptane/EtOAc 4:1) was achieved using UV trace of eluting products. By TLC analysis of fractions, no difference could be determined between the products. However, UV analysis of the product-containing fractions showed two distinct products and traces of starting material, collected individually, to give both benzaldehyde azetidinol diastereoisomers: *epi*-**13g** as a clear crystalline solid (60 mg, 19%) and **13g** as a pale yellow syrup (171 mg, 53%). A crystal of *epi*-**13g** for X-ray crystallographic analysis was obtained by slow evaporation from $CDCl_3$. **Minor diastereoisomer** (*epi*-**13g**): R_f 0.45 (pet ether/EtOAc 3:2); mp 145–148 °C; IR (neat/cm^{-1}) 3444 w, 2964 w, 2928 w, 1486 s, 1362 w, 1180 w, 1106 m, 1008 m, 703 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.28 (5H, m, Ar), 5.76 (1H, d, J = 1.8 Hz, PhCH(OH)), 4.95 (1H, ddd, J = 3.3, 1.9, 1.8 Hz, NCH), 4.44 (1H, dt, J = 6.6, 3.3 Hz, CHOH), 4.29 (1H, ddd, J = 11.0, 6.6, 1.8 Hz, $NCH_{cis}H_{trans}$), 4.09 (1H, dd, J = 11.0, 3.3 Hz, $NCH_{cis}H_{trans}$), 3.48 (1H, s, OH), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8 (C=S), 139.3 (Ar), 128.5 Ar), 127.8 (Ar), 126.3 (Ar), 82.5 (NCH), 70.8 (PhCH(OH)), 64.9 (NCH_2), 62.4 (CHOH), 43.7 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$); LRMS (ESI$^+$) 302.10 ([M + Na]$^+$ 85%); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2S$ 302.1185, found 302.1181; for X-ray data, see Supporting Information. **Major diastereoisomer** (**13g**): R_f 0.45 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3354 br, 2966 w, 2924 wm 1455 s, 1433 m, 1364 w, 1244 w, 1130 w, 1041 w, 704 m; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35–7.26 (5H, m, Ar), 5.80 (1H, d, J = 5.8 Hz, CHOH), 5.73 (1H, d, J = 4.3 Hz, PhCH(OH)), 5.72 (1H, dd, J = 4.9, 4.3 Hz, PhCH(OH), 4.62 (1H, ddd, J = 4.9, 2.6, 2.0 Hz, NCH), 4.03 (1H, ddt, J = 6.3, 5.8, 2.6 Hz, CHOH), 3.84 (1H, dd, J = 11.3, 2.6 Hz, $NCH_{cis}H_{trans}$), 3.36 (1H, ddd, J = 11.3, 6.3, 2.0 Hz, $NCH_{cis}H_{trans}$), 1.15 (9H, s, $(C(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 209.6 (C=S), 140.8 (Ar), 127.5 (Ar), 127.1 (Ar), 126.3 (Ar), 80.0 (NCH), 65.5 (NCH_2), 65.2 (PhCH(OH), 60.8 (CHOH), 42.7 ($C(CH_3)_3$), 29.2 ($C(CH_3)_3$); LRMS (ESI$^+$) 302.10 ([M + Na)$^+$] 70%); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2S$ 302.1185, found 302.1186.

1-(2-((4-Chlorophenyl)(hydroxy)methyl)-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (13h). *p*-Chlorobenzaldehyde (122 mg, 0.87 mmol) was used following General Procedure A, but on half the scale. Purification (Si gel, pet ether/EtOAc 9:1→4:1) gave both aldehyde azetidinol diastereoisomers: *epi*-**13h** as a pale yellow syrup (31 mg, 34%) and **13h** as a pale yellow syrup (43 mg, 47%). **Minor diastereoisomer** (*epi*-**13h**): R_f 0.54 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3254 br, 2969 w, 1470 s, 1244 w, 1127 m, 1090 m, 1007 m, 911 m, 854 w, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (4H, m, Ar), 5.65 (1H, s, *p*-ClPhCH(OH)), 4.91 (1H, dt, J = 3.2, 2.0 Hz, NCH), 4.35 (1H, dt, J = 6.5, 3.2 Hz, CHOH), 4.26 (1H, ddd, J = 11.0, 6.5, 2.0 Hz, $NCH_{cis}H_{trans}$), 4.09 (1H, dd, J = 11.0, 3.2 Hz, $NCH_{cis}H_{Trans}$), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9 (C=S), 137.7 (Ar), 133.6 (Ar), 128.6 (Ar), 127.8 (Ar), 82.2 (NCH), 70.5 (*p*-ClPhCH(OH)), 64.9 (NCH_2), 62.3 (CHOH), 43.7 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (ESI$^+$) 336.10 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}ClNNaO_2S$ 336.0795, found 336.0800. **Major diastereoisomer** (**13h**): R_f 0.37 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3363 br, 2972 w, 1459 s, 1365 w, 1131 m, 1091 m, 906 s, 791 m, 727 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (4H, s, Ar), 5.47 (1H, d, J = 6.8 Hz, *p*-ClPhCH(OH), 4.87 (1H, dd, J = 6.8, 1.8 Hz, NCH), 4.14–4.06 (3H, m, CHOH and $NCH_{cis}H_{trans}$), 1.30 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (C=S), 137.6 (Ar), 134.0 (Ar), 128.6 (Ar), 128.3 (Ar), 81.5 (NCH), 71.0 (*p*-ClPhCH(OH)), 64.4 (NCH_2), 62.4 (CHOH), 43.8 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$); LRMS (ESI$^+$) 336.10 ([M + Na]$^+$, 82%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}ClNNaO_2S$ 336.0795, found 336.0800.

Methyl 1-(2,2-dimethylpropanethioyl)-3-[(methoxycarbonyl)oxy]azetidine-2-carboxylate (13i). Methyl cyanoformate (276 μL, 3.46 mmol) was used following General Procedure A. Purification (Si gel, pet ether/EtOAc 9:1→4:1) gave azetidine diester **13i** as a pale yellow syrup which solidified on standing (115 mg, 68% 93:7 *trans*/*cis*,[13] dr determined by integration of δ_H 5.01 and 4.56): R_f 0.70 (pet ether/EtOAc 3:2); mp 85–87 °C; IR (neat/cm^{-1}) 2960 w, 1739 s, 1430 s, 1295 m, 1272 m, 1199 m, 1158 m, 992 m, 931 m, 790 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, dt, J = 6.7, 3.4 Hz, CHO), 4.96 (1H, m, NCH), 4.89 (1H, ddd, J = 11.1, 6.7, 1.9 Hz, $NCH_{cis}H_{trans}$), 4.44 (1H, dd, J = 11.1, 3.4 Hz, $NCH_{cis}H_{trans}$), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3 (C=S), 167.0 (NCHC(O)), 154.3 (CHOC(O)), 72.0, (NCH), 66.5 (CHO), 61.9 (NCH_2), 55.5 (OCH_3), 52.6 (OCH_3), 43.2 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$); LRMS (ESI$^+$) 312.1 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{12}H_{19}NNaO_5S$ 312.0876, found 312.0868.

2-Benzylazetidin-3-ol hydrochloride (14). To a solution of benzylated azetidinol **13d** (69 mg, 0.26 mmol) in THF at 0 °C were added TMEDA (196 μL, 1.31 mmol) and MeLi (873 μL, 1.50 M in Et_2O, 1.31 mmol). After 4 h, the reaction mixture was quenched with MeOH (few drops) and concentrated to dryness under reduced pressure. The crude reaction mixture was dissolved in a minimum of MeOH and loaded onto a SCX-2 ion exchange column. The column was washed through with CH_2Cl_2 (20 mL) and collected. The amine product was released with NH_3 (10 mL, 7 M in MeOH) followed by CH_2Cl_2 (20 mL) and collected. The basic fractions were concentrated to dryness under reduced pressure, redissolved in MeOH (2 mL), and treated with HCl (2 M in Et_2O, 2 mL), followed by concentrating to dryness under reduced pressure to isolate the crude hydrochloride salt. The crude product was suspended in acetone (2 mL) and decanted to remove organic impurities, giving azetidine hydrochloride salt **14** as a pale yellow solid (48 mg, 92%): mp 127–131 °C; IR (neat/cm^{-1}) 3306 br, 2956 w, 2938 w, 2458 m, 2184 br, 1454 w, 1173 m, 1117 m, 1031 w, 977 w, 747 m, 702 s; ^{1}H NMR (400 MHz, CD_3OD) δ 7.38–7.25 (5H, m, Ar), 4.53 (1H, q, J = 7.4 Hz, CHOH), 4.40 (1H, ddd, J = 8.9, 7.4, 6.8 Hz, NCH), 4.07 (1H, dd, J = 10.5, 7.4 Hz, NCHH), 3.74 (1H, dd, J = 10.5, 7.4 Hz, NCHH), 3.24 (1H, dd, J = 14.4, 6.8 Hz, CHHPh), 3.17 (1H, dd, J = 14.4 8.9 Hz, CHHPh); ^{13}C NMR (100 MHz, CD_3OD) δ 136.5 (Ar), 130.2 (Ar), 130.1 (Ar), 128.5 (Ar), 73.0 (NCH), 68.4 (CHOH), 53.1, (NCH_2), 38.1 (CH_2Ph); LRMS (ESI$^+$) 164.09 ([M − HCl + H)]$^+$, 40%); HRMS (ESI$^+$) calcd for $C_{10}H_{14}NO$ 164.1070, found 164.1070.

dx.doi.org/10.1021/jo3025225 | J. Org. Chem. 2013, 78, 1098–1106

1-(2-Benzyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropan-1-one (15). To an ice-cold stirred solution of AcOH (3 mL) and H_2O_2 (4 mL, 35% in H_2O) was added benzylated azetidinol **13d** (59 mg, 0.24 mmol) in CH_2Cl_2 (1 mL). After 4 h at 0 °C, the reaction mixture was poured onto saturated aq $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (10 mL), H_2O (10 mL), then brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure to give pivalamide **15** as a colorless syrup (45 mg, 81%): R_f 0.23 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 2359 br, 2963 w, 1595 s, 1412 m, 1364 w, 1232 w, 1129 w, 736 w, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.20 (5H, m, Ar), 4.44 (1H, ddd, J = 7.8, 3.7, 3.3 Hz, NCH), 4.18 (1H, dt, J = 6.8, 3.7 Hz, CHOH), 4.10 (1H ddd, J = 9.3, 6.8, 1.0 Hz, $NCH_{cis}H_{trans}$), 3.95 (1H, dd, J = 9.3, 3.7 Hz, $NCH_{cis}H_{trans}$), 3.20, (1H, dd, J = 13.9, 3.3 Hz, CHHPh), 3.02 (1H, dd, J = 13.9, 7.8 Hz, CHHPh), 1.15 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1 (C(O)), 136.7 (Ar), 129.6 (Ar), 128.3 (Ar), 126.4 (Ar), 71.7 (NCH), 65.7 (CHOH), 60.1 (NCH_2), 38.7 ($C(CH_3)_3$), 36.7 (CH_2Ph), 27.0 ($C(CH_3)_3$); LRMS (ESI$^+$) 270.12 ([M + Na]$^+$, 78%); HRMS (ESI$^+$) calcd for $C_{15}H_{21}NNaO_2$ 270.1465, found 270.1466.

2-Deutero-1-(2,2-dimethylpropanethioyl)-azetidin-3-yl trifluoromethanesulfonate (16). To a stirred solution of deuterated adduct *cis*-**13a** (417 mg, 2.39 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DIPEA (538 μL, 3.11 mmol) followed by dropwise addition of Tf_2O (482 μL, 2.87 mmol). After 30 min, MeOH (1 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 19:5→9:1) gave triflate **16** as a pale yellow syrup which solidified on standing (601 mg, 82%): R_f 0.27 (pet ether/EtOAc 3:2); mp 55−57 °C; IR (neat/cm^{-1}) 2981 w, 2907 w, 1470 m, 1441 m, 1353 s, 1218 m, 1171 m, 986 m, 914 m, 849 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, td, J = 6.4, 3.8 Hz, CHO), 4.91 (0.95 H, dd, J = 11.9, 6.9 Hz, $NCH_{cis}H_{trans}$), 4.73−4.62 (1.51H, m, $NCH_{cis}H_{trans}$), 4.46 (0.58H, ddd, J = 13.8, 3.8, 2.1 Hz, $NCH_{cis}H_{trans}$), 1.36 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7 (C═S), 118.3 (Q, J = 320 Hz, CF_3), 72.9 (CHO), 72.9 (t, J = 5 Hz, CHO), 62.7 (NCH_2), 62.4 (T, J = 23 Hz, NCHD), 61.7 (NCH_2), 61.4 (T, J = 23 Hz, NCHD), 43.6 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$); δ_F (377 MHz, $CDCl_3$) −74.7 (CF_3); LRMS (FI$^+$) 306.04 ([M]$^+$, 100%); HRMS (FI$^+$) calcd for $C_9H_{13}DF_3NO_3S_2$ 306.0430, found 306.0432.

2-Deutero-1-(2,2-dimethylpropanethioyl)azetidin-3-yl acetate (17). To a stirred solution of triflate **16** (586 mg, 1.91 mmol) in DMF (10 mL) was added NaOAc (5.3 g, 65 mmol), and the reaction mixture was heated to 70 °C. After 16 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 9:1→4:1) gave acetate **17** as a colorless syrup (355 mg, 86%): R_f 0.41 (pet ether/EtOAc 4:1); IR (neat/cm^{-1}) 2968 w, 1741 s, 1462 m, 1437 m, 1364 w, 1225 s, 1143 m, 731 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, dt, J = 6.8, 3.8 Hz, CHO), 4.81 (0.59H, ddd, J = 11.4, 6.8, 1.3 Hz, $NCH_{cis}H_{trans}$), 4.55 (0.60H, ddd, J = 13.4, 6.8, 1.3 Hz, $NCH_{cis}H_{trans}$), 4.35 (0.93H, dd, J = 11.4, 3.8 Hz, $NCH_{cis}H_{trans}$), 4.23 (0.91H, dd, J = 13.4, 3.8 Hz, $NCH_{cis}H_{trans}$), 2.12 (3H, s, $OC(O)CH_3$), 1.34 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6 (C═S), 170.4 (C(O)), 63.3 (NCH_2), 63.0 (T, J = 23 Hz, NCHD), 62.0 (CHO), 62.0 (t, J = 9 Hz, CHO), 61.8 (NCH_2), 61.6 (T, J = 23 Hz, NCHD), 43.3 ($C(CH_3)_3$), 29.7 ($C(CH_3)_3$), 20.6 (CH_3); LRMS (ESI$^+$) 217.1 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{10}H_{16}DNNaO_2S$ 239.0935, found 239.0928.

1-(2-Deutero-3-(hydroxy)-azetidin-1-yl)-2,2-dimethylpropane-1-thione (*trans*-13a). To a stirred solution of acetate **17** (350 mg, 1.62 mmol) in MeOH (10 mL) was added NaOMe (15 drops, 30% in MeOH). After 10 min, the reaction mixture was concentrated to dryness under reduced pressure. The residue was washed with aq HCl (1 M, 10 mL) and extracted with EtOAc (20 mL), and the organic layer was washed with H_2O (10 mL), then brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 3:2→2:3) gave azetidin-3-ol *trans*-**13a** as a colorless syrup which solidified on standing (186 mg, 66%, 100% D, 88:12 *trans*/*cis*,[13] dr determined by integration of δ_H 4.70 + 4.48 and 4.32 + 4.10): R_f 0.27 (pet ether/EtOAc 3:2); mp 54−56 °C; IR (neat/cm^{-1}) 3359 br, 2968 w, 1469 s, 1364 w, 1255 w, 1138, 1005 m, 951 w, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (0.56 H, ddd, J = 11.1, 6.6, 1.5 Hz, $NCH_{cis}H_{trans}$), 4.65 (1H, dt, J = 6.6, 3.9 Hz, CHOH), 4.48 (0.56H, ddd, J = 12.9, 6.6, 1.5 Hz, $NCH_{cis}H_{trans}$), 4.32 (0.94H, dd, J = 11.1, 3.9 Hz, $NCH_{cis}H_{trans}$), 4.10 (0.94H, dd, J = 12.9, 3.9 Hz, $NCH_{cis}H_{trans}$), 3.14 (1H, br, OH), 1.33 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (C═S), 65.8 (NCH_2), 65.5 (T, J = 23 Hz, NCHD), 65.5 (NCH_2), 65.2 (T, J = 23 Hz, NCHD), 59.8 (CHOH), 59.8 (t, J = 10 Hz, CHOH), 43.2 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (ESI$^+$) 175.2 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_8H_{14}DNNaOS$ 197.0829, found 197.0825.

Lithiation−Deuteration of *cis*-13a: 1-(2,4-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,4Dcc) and 1-(2,2-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,2D). To a stirred solution of azetidinol *cis*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, CD_3OD (52 μL, 1.45 mmol) was added, and the reaction mixture was stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **18** as a pale yellow syrup (50 mg, 95%, 99% 2D, 62:38 2,4-:2,2-,[13] dr determined by integration of δ_H 4.66 + 4.42 and 4.29 + 4.04 in comparison to *cis*-**13a**):[13] IR (neat/cm^{-1}) 3365 br, 2967 w, 2932 w, 1465 s, 1364 w, 1134 s, 1007 m, 913 m, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (0.76H, dd, J = 11.1, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.59 (1H, t, J = 6.6 Hz, CHOH), 4.42 (0.76H, dd, J = 12.9, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.29 (0.23H, dd, J = 11.1, 3.5 Hz, $NCH_{cis}H_{trans}$), 4.04 (0.26H, dd, J = 12.9, 3.5 Hz, $NCH_{cis}H_{trans}$), 3.76 (1H, br s, OH), 1.29 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (C═S), 65.8 (NCH_2), 65.5 (T, J = 23 Hz, NCHD), 65.4 (NCH_2), 65.1 (T, J = 23 Hz, NCHD), 59.5 (CHOH), 59.5 (t, J = 8 Hz, CHOH), 43.1 ($C(CH_3)_3$), 29.5 ($C(CH_3)_3$); LRMS (ESI$^+$) 198.08 ([M + Na]$^+$, 93%); HRMS (FI$^+$) calcd for $C_8H_{13}D_2NOS$ 175.1000, found 175.1001.

Lithiation−Deuteration of *trans*-13a: 1-(2,4-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,4Dtc) and 1-(2,2-Dideutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (18-2,2D). To a stirred solution of azetidinol *trans*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, CD_3OD (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **18** as a pale yellow syrup (45 mg, 90%, 91% 2D, 82:18 2,4-:2,2-,[13] dr determined by integration of δ_H 4.69 + 4.46 and 4.31 + 4.08 in comparison to *trans*-**13a**):[13] IR (neat/cm^{-1}) 2251 br, 2968 w, 1467 s, 1364 w, 1139 m, 1112 m, 1007 w, 912 w, 730 s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (0.47H, dd, J = 11.1, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.64−4.60 (1H, m, CHOH), 4.46 (0.49H, dd, J = 12.9, 6.6 Hz, $NCH_{cis}H_{trans}$), 4.31 (0.56H, dd, 11.1, 3.9 Hz, $NCH_{cis}H_{trans}$), 4.08 (0.57H, dd, J = 12.9, 3.9 Hz, $NCH_{cis}H_{trans}$), 3.46 (1H, br, OH), 1.32 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (C═S), 65.8 (NCH_2), 65.5 (T, J = 23 Hz, NCHD), 65.5 (T, J = 23 Hz, NCHD), 65.5 (NCH_2), 65.2 (T, J = 23 Hz, NCHD), 65.1 (T, J = 23 Hz, NCHD), 59.7 (CHOH), 59.7 (t, J = 8 Hz, CHOH), 59.7 (t, J = 8 Hz, CHOH), 43.2 ($C(CH_3)_3$), 29.6 ($C(CH_3)_3$); LRMS (ESI$^+$) 198.1

dx.doi.org/10.1021/jo3025225 | J. Org. Chem. 2013, 78, 1098−1106

([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_8H_{13}D_2NNaOS$ 198.0892, found 198.0893.

Lithiation−Protonation of *cis*-13a: 1-(2-Deutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (13a). To a stirred solution of azetidinol *cis*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, MeOH (58 μL, 1.43 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol **13a** as a pale yellow syrup (50 mg, quant, 100% D, 64:36 *cis*/*trans*,[13] dr determined by integration of δ_H 4.67 + 4.42 and 4.28 + 4.04). Characterization data are the same as that of *cis*-**13a**, with the exception of two additional peaks in the ^{13}C NMR spectrum: 65.5 (T, *J* = 23 Hz, NCHD), 65.2 (T, *J* = 23 Hz, NCHD).

Lithiation−Protonation of *trans*-13a: 1-(2-Deutero-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (*trans*-13a). To a stirred solution of azetidinol *trans*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.40 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, MeOH (52 μL, 1.45 mmol) was added and the reaction mixture stirred for 10 min. The cold bath was removed, and the reaction mixture was stirred for another 10 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) then brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure to give azetidinol *trans*-**13a** as a pale yellow syrup (43 mg, 86%, 100% D, 87:13 *trans*/*cis*,[13] dr determined by integration of δ_H 4.70 + 4.48 and 4.32 + 4.10). Characterization data are the same as that of *trans*-**13a**.

Lithiation−Benzylation of *cis*-13a: 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_c$-4Bn$_t$, 19-2D$_t$-4Bn$_t$) and 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_c$-2Bn$_t$). To a stirred solution of azetidinol *cis*-**13a** (50 mg, 0.29 mmol) in THF (1 mL) at −78 °C under argon was added TMEDA (261 μL, 1.74 mmol). *s*-BuLi (614 μL, 1.4 M in cyclohexane/hexane (92/8), 0.86 mmol) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, BnBr (102 μL, 0.86 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to room temperature and stirred for another 30 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, heptane/EtOAc 1:0→2:3) gave azetidinol **19** as a pale yellow syrup (52 mg, 69%, 100% D, 61:6:33 **2D$_c$-4Bn$_t$/2D$_t$-4Bn$_t$/2D$_c$-2Bn$_t$**[13] dr determined by integration of δ_H 4.80, 4.18 and 4.08): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3364 br, 3027 w, 2967 w, 1454 s, 1434 m, 1395 w, 1135 m, 1096 m, 910 m, 730 s, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (5H, m, Ar), 4.80 (0.67H, ddd, *J* = 7.6, 3.5, 2.9 Hz, NCH) 4.24 (1H, dd, *J* = 6.3, 2.9 Hz, C<u>H</u>OH), 4.18 (0.94H, dd, *J* = 11.1, 6.3 Hz, NCH$_{Cis}$<u>H</u>$_{Trans}$), 4.08 (0.38H, dd, *J* = 11.1, 2.9 Hz, NC<u>H</u>$_{Cis}$H$_{Trans}$), 3.43 (1H, dd, *J* = 13.9, 3.5 Hz, C<u>H</u>HPh), 3.35 (0.3H, d, J = 13.9 Hz, CDC<u>H</u>HPh), 3.36 (0.7H, dd, *J* = 13.9, 7.6 Hz, CH<u>H</u>Ph), 2.63 (1H, br, OH), 1.31 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8 (C(S)), 136.5 (Ar), 129.7 (Ar), 128.4 (Ar), 126.7 (Ar), 77.5 (NCH), 65.3 (CHOH), 64.7 (NCH$_2$), 64.4 (T, *J* = 23 Hz, NCDH), 43.6 (<u>C</u>(CH$_3$)$_3$), 33.9 (<u>C</u>H$_2$Ph), 29.7 (C(<u>C</u>H$_3$)$_3$); LRMS (ESI$^+$) 287.12 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}DNNaOS$ 287.1299, found 287.1296.

Lithiation−Benzylation of *trans*-13a: 1-(4-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_t$-4Bn$_t$, 19-2D$_c$-4Bn$_t$) and 1-(2-Deutero-3-hydroxy-2-phenylazetidin-1-yl)-2,2-dimethylpropane-1-thione (19-2D$_c$-2Bn$_t$). To a stirred solution of azetidinol *trans*-**13a** (26 mg, 0.15 mmol) in THF (0.5 mL) at −78 °C under argon was added TMEDA (135 μL, 0.90 mmol). *s*-BuLi (333 μL, 0.45 mmol, 1.35 M in cyclohexane/hexane (92/8)) was added very slowly dropwise to the reaction mixture over 5 min. After 30 min, BnBr (54 μL, 0.45 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was warmed to room temperature and stirred for another 30 min, quenched with aq HCl (1 M, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 4:1→2:3) gave azetidinol **19** as a pale yellow syrup (19 mg, 48%, 100% D, 60:10:30 **2D$_t$-4Bn$_t$/2D$_c$-4-Bn$_t$/2D$_c$-2Bn$_t$**[13] dr determined by integration of δ_H 4.81, 4.19 and 4.09): R_f 0.64 (pet ether/EtOAc 3:2); IR (neat/cm^{-1}) 3373 br, 2967 w, 1454 s, 1435 m, 1129 m, 1091 m, 997 m, 910 m, 730 s, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (5H, m, Ar), 4.81 (0.70H, dt, *J* = 6.6, 2.8 Hz, NCH), 4.25 (1H, m, C<u>H</u>OH), 4.19 (0.40H, dd, *J* = 11.1, 6.8 Hz, NCH$_{Cis}$<u>H</u>$_{Trans}$), 4.09 (0.90H, dd, *J* = 11.1, 2.8 Hz, NC<u>H</u>$_{Cis}$H$_{Trans}$), 3.43 (1H, dd, *J* = 13.9, 3.5 Hz, C<u>H</u>HPh), 3.35 (0.3H, d, J = 13.9 Hz, CDC<u>H</u>HPh), 3.36 (0.7H, dd, *J* = 13.9, 7.6 Hz, CH<u>H</u>Ph), 2.52 (1H, br, OH), 1.32 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7 (C(S)), 136.5 (Ar), 129.7 (Ar), 128.4 (Ar), 126.8 (Ar), 77.5 (NCH), 65.3 (CHOH), 64.7 (NCH$_2$), 64.4 (T, *J* = 23 Hz, NCDH), 43.6 (<u>C</u>(CH$_3$)$_3$), 33.9 (<u>C</u>H$_2$)Ph), 29.7 (C(<u>C</u>H$_3$)$_3$); LRMS (ESI$^+$) 265.1 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{15}H_{20}DNNaOS$ 287.1299, found 287.1290.

2-Benzyl-1-(2,2-dimethylpropanethioyl)azetidin-3-yl acetate (20). To a stirred solution of benzyl adduct **13d** (412 mg, 1.56 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added DIPEA (351 μL, 2.02 mmol) followed by dropwise addition of Tf_2O (289 μL, 1.72 mmol). After 30 min, MeOH (1 mL) was added and the reaction mixture concentrated to dryness under reduced pressure. The crude triflate was dissolved in DMF (5 mL) and to it was added NaOAc (1.28 g, 16 mmol) and the reaction mixture was heated to 70 °C. After 2 h, the reaction mixture was cooled to rt, washed with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. Purification (Si gel, pet ether/EtOAc 39:1→9:1) gave inverted acetate **20** as a colorless syrup (245 mg, 51%): R_f 0.44 (pet ether/EtOAc 9:1); IR (neat/cm^{-1}) 2968 w, 2872 w, 1742 s, 1455 m, 1431 m, 1364 w, 1224 s, 1155 w, 1111 m, 1007 w, 910 m, 729 s, 700 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.19 (5H, m, Ar), 5.36−5.28 (2H, m, NCH and C<u>H</u>OH), 4.75 (1H, ddd, *J* = 10.9, 7.3, 1.0 Hz, NC<u>H</u>$_{trans}$H$_{cis}$), 4.20 (1H, ddd, *J* = 10.9, 5.3, 1.5 Hz, NCH$_{trans}$<u>H</u>$_{cis}$), 3.78 (1H, dd, *J* = 13.8, 1.6 Hz, C<u>H</u>HPh), 3.30 (1H, dd, *J* = 13.8, 9.2 Hz, CH<u>H</u>Ph), 2.09 (3H, s, CH$_3$), 1.32 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7 (C═S), 170.0 (C═O), 137.3 (Ar), 129.5 (Ar), 128.1 (Ar), 126.4 (Ar), 72.4 (NCH), 63.6 (CHOH), 63.3 (NCH$_2$), 43.6 (<u>C</u>(CH$_3$)$_3$), 30.4 (N<u>C</u>H$_2$Ph), 29.6 (C(<u>C</u>H$_3$)$_3$), 20.6 (CH$_3$); LRMS (ESI$^+$) 306.2 ([M + H]$^+$, 100%); HRMS (ESI$^+$) calcd for $C_{17}H_{23}NNaO_2S$ 328.1342, found 328.1337.

1-(2-Benzyl-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (*cis*-13d). To a stirred solution of inverted acetate **20** (245 mg, 0.80 mmol) in MeOH (3 mL) was added NaOMe (10 drops, 30% in MeOH). After 1 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was washed with aq HCl (1 M, 10 mL) and extracted with CH_2Cl_2 (10 mL), and the organic layer was washed brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure gave *cis*-benzyl adduct *cis*-**13d** as a pale orange syrup which solidified on standing (184 mg, 87%); diastereoselectivity determined by ^{1}H NMR coupling constant analysis: R_f 0.47 (pet ether/EtOAc 4:1); mp 101−103 °C; IR (neat/cm^{-1}) 3368 br, 2996 w, 2964 w, 2929 w, 1468 s, 1435 s, 1357 w, 1253 w, 1149 m, 1109 m, 1037 w, 984 w, 829 w, 746 m, 702 m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (5H, m, Ar), 5.17 (1H, dddd, *J* = 10.4, 7.3, 2.4, 2.0 Hz, NCH), 4.77 (1H, td, *J* = 7.3, 5.6 Hz, C<u>H</u>OH), 4.65 (1H, dd, *J* = 10.8, 7.3 Hz, NC<u>H</u>$_{trans}$H$_{cis}$), 4.23 (1H, ddd, *J* = 10.8, 5.6, 2.0 Hz, NCH$_{trans}$<u>H</u>$_{cis}$), 3.83 (1H, dd, *J* = 13.7, 2.4 Hz, C<u>H</u>HPh), 3.31 (1H, dd, *J* = 13.4, 10.4 Hz, CH<u>H</u>Ph), 2.03 (1H, br, OH), 1.34 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (C═S), 138.2 (Ar), 129.4 (Ar), 128.5 (Ar), 126.4 (Ar), 74.5 (NCH), 64.7 (NCH$_2$), 62.5 (CHOH), 43.5 (<u>C</u>(CH$_3$)$_3$), 29.6 (C(<u>C</u>H$_3$)$_3$); LRMS

dx.doi.org/10.1021/jo3025225 | J. Org. Chem. 2013, 78, 1098−1106

(ESI+) 286.2 ([M + Na]+, 100%); HRMS (ESI+) calcd for $C_{15}H_{21}NNaOS$ 286.1236, found 286.1244.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all compounds, ^1H analysis of deuterated adducts and X-ray data for *epi*-**13g**. 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.

■ ACKNOWLEDGMENTS

We thank AstraZeneca and the EPSRC for funding, and L. Campbell and P. Schofield (AstraZeneca) for helpful discussions.

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(16) By ^1H NMR comparison with **13d** and *cis*-**13d**, the latter being available from **13d** through the corresponding inverted acetate **20** by an identical alcohol inversion sequence to that used for *trans*-**10a** (see Experimental Section).

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