Heterocycles

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Lithiation–Electrophilic Substitution of *N*-Thiopivaloylazetidine**

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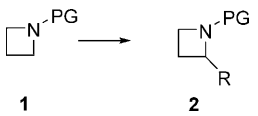
Owing to the widespread importance of amines, advances in their synthesis and elaboration continue to constitute a major area of chemical research.[1] The main strategies that have been employed for the convergent assembly of α-branched amines are reductive amination, alkene hydroamination, C–H insertion by a nitrogen source, carbanion addition to imines, and the reaction of an α-C–H bond of a suitably N-protected/activated amine. Whilst several ways exist to achieve the latter strategy with saturated azacycles of various ring size,[2] there is currently no general method of achieving this with an azetidine (**1**) to give a 2-substituted azetidine (**2**, PG = protecting/activating group; Scheme 1), particularly in an enantioselective manner. Substituted azetidines are often challenging to synthesize but have significance and current interest as bioactive entities; they have also been used as ligands in metal-catalyzed transformations and as chiral auxiliaries.[3] Herein, we report a promising route to 2-substituted azetidines from azetidine itself, the latter being readily available in multi-kilogram quantities.[4]



1 **2**

Scheme 1. Substitution at the C2 position of *N*–PG azetidine **1**. PG = protecting/activating group.

There are few previous studies concerning the reaction of the α-C–H bonds of N-substituted azetidine. The two-step introduction of some nucleophiles at the C2-position of *N*-tosylazetidine (**1**, PG = Ts) has been achieved using anodic C2 acetoxylation,[5] whilst the attempted direct C–H insertion of *N*-Boc-azetidine (**1**, PG = Boc) using methyl phenyldiazoacetate under Rh^{II} catalysis formed a complex mixture of products (normal-sized azacycles were much more effective).[6] Within the large body of work on metalation–electrophile-trapping at the position α to the nitrogen atom,[2] to the best of our knowledge there are only two isolated examples of trapping on an azetidine ring: the reaction of *N*-nitrosoazetidine (**1**, PG = NO) with LDA (LDA = lithium diisopropylamide; THF, −78 °C), followed by addition of benzophenone gave the corresponding tertiary alcohol (65% yield),[7] and the reaction of *N*-(triphenylacetyl)azetidine (**1**, PG = $COCPh_3$) with *t*BuLi (THF, −40 °C) and benzaldehyde gave the corresponding secondary alcohol (62% yield, d.r. not reported).[8] However, we decided against examining these azetidines in more detail owing to several drawbacks with both methods; carcinogenicity and poor prospects for asymmetric induction were concerns with the former, whilst disadvantages of the latter included the use of a high molecular weight triphenylacetyl group and the requirement of *t*BuLi to achieve the metalation, which was considered problematic for the later development of an asymmetric variant of the reaction.[9] Furthermore, complications have been observed from *ortho*-lithiation at the triphenylacetyl group followed by a carbamoyl group 1,3-shift,[8] and in our hands the reported metalation proved problematic.

Initially, we investigated *N*-Boc-azetidine (**1**, PG = Boc)[10] because of the likelihood of facile deprotonation, by analogy to its higher[11] and lower ring-size homologues.[12] However, *N*-Boc-azetidine (**1**, PG = Boc) was found to be inert to lithium amides (LDA or LTMP, LTMP = lithium 2,2,6,6-tetramethylpiperidide) that had previously been used to lithiate related aziridines. The use of *s*BuLi was also unsatisfactory; no reaction or partial lithiation (36% [D] incorporation by GC-MS using CD_3OD as the electrophile) was seen after 25 minutes at −78 °C in diethyl ether or tetrahydrofuran, respectively, and attempts to induce greater conversion in either solvent by warming or by adding tetramethylethylenediamine (TMEDA) as an additive only led to complex mixtures of products (including for the latter case in tetrahydrofuran, significant attack on the carbamoyl group).[13] In contrast to the corresponding aziridine,[14] *N*-sulfinylazetidine (**1**, PG = S*O*t*Bu*) mainly underwent decomposition with lithium amide or organolithium reagents, whereas *N*-*tert*-butylsulfonyl- and *N*-(diethylphosphonyl)azetidines (**1**, PG = SO_2*t*Bu and $PO(OEt)_2$, respectively) resisted lithiation under a variety of conditions. At this stage, a review of the less commonly used N-protecting/activating groups for deprotonation at the position α to the nitrogen atom[2] led us to consider the thiopivaloyl group, even though the literature was not encouraging: Seebach and Lubosch originally reported that out of several secondary amine-derived thiopivalamides studied (including that from piperidine), only the thiopivalamide that was derived from dimethylamine could be lithiated (*s*BuLi/TMEDA, THF, −78 °C) and trapped with electrophiles.[15] To examine this chemistry with azetidine (**3**), the derived crude pivalamide was treated with P_2S_5 to give

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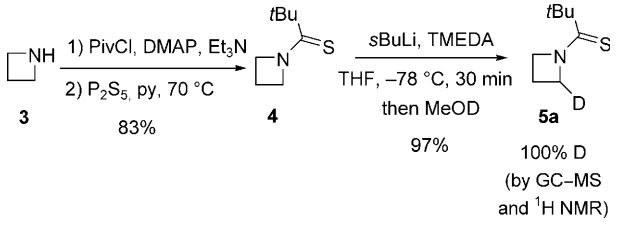
thioamide **4** following simple distillation (83% from **3**, Scheme 2). Remarkably, and in stark contrast to our observations with the other azetidines discussed above, thioamide **4** underwent very clean lithiation–deuteration, to give 2-deuterated azetidine **5a** in excellent yield (Scheme 2). The importance of the thioamide functionality to the success of this transformation was underlined when α lithiation of the precursor pivalamide was attempted: only 2,2,4-trimethylhexan-3-one, which arises from the attack of *s*BuLi at the amide carbonyl carbon atom, was observed (LTMP returned only the starting pivalamide).

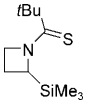
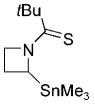
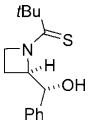
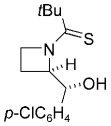
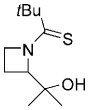
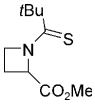
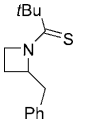
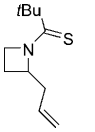
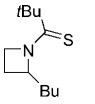


Scheme 2. Preparation, lithiation, and deuteration of thioamide **4**. py = pyridine, DMAP = 4-dimethylaminopyridine, Piv = pivaloyl.

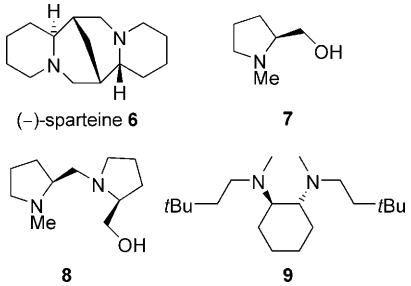
Next, the scope of electrophile incorporation into thioamide **4** was investigated (Table 1). Silylation and stannylation were equally viable (Table 1, entries 1 and 2), as were reactions using carbonyl-based electrophiles (Table 1, entries 3–6); the excellent yield found with acetone (94%; Table 1, entry 5) indicates that potentially competing enolization is not a problem. For entries 3 and 4, single diastereomers were observed; the product in entry 3 was established by X-ray crystallographic analysis to have an *R**,*R** configuration (see the Supporting Information). This excellent diastereoselectivity is noteworthy, given the absence of such selectivity when using aldehydes with α-lithiated aziridines,[14] *N*-Boc-pyrrolidine, or *N*-Boc-piperidines.[11] Alkylation of dipole-stabilized organolithium compounds using alkyl halides can be inefficient (ascribed to the intervention of single-electron transfer processes),[2b,11] but thioamide **4** was found to undergo methylation, allylation, benzylation, and butylation in uniformly high yields (79–93%, entries 7–10). Using MeLi, we also established the viability of removing the thiopivaloyl group from an α-substituted azetidine (81% from **5i**, isolated as the hydrochloride salt; conversion into the corresponding pivalamide, in 93% yield from **5i**, was also achieved with CH_3CO_3H).[15]

Possible extension of this procedure to incorporate electrophiles onto the protected aziridine in an enantiocontrolled fashion was first examined by replacing TMEDA with the lupine alkaloid (−)-sparteine (**6**; Scheme 3); this chiral ligand has previously been shown to be effective in several asymmetric lithiation reactions.[9,16,17] When methyl iodide was used as the electrophile in diethyl ether, methylated azetidine (*R*)-**5h** was obtained in an e.r. of 61:39 (99% conversion by GC-MS; Table 2, entry 1).[18] The stereochemistry of the major enantiomer was established by comparison with material synthesized from commercial *N*-Boc-(*S*)-azetidine-2-carboxylic acid (see the Supporting Information), and

Table 1: Scope of electrophile incorporation into thioamide **4**.

Entry	Electrophile	Substituted azetidine		Yield [%]
1	Me_3SiCl		**5b**	91
2	Me_3SnCl		**5c**	86
3	PhCHO		**5d**	87[a]
4	*p*-ClC_6H_4CHO		**5e**	68[b]
5	$(CH_3)_2CO$		**5f**	94
6	CO_2		**5g**	61[c]
7	MeI		**5h**	93
8	BnBr		**5i**	81
9	CH_2CHCH_2Br		**5j**	79
10	BuBr		**5k**	83

[a] Isolated as a single diastereomer (*R**,*R**). [b] Stereochemistry assigned by analogy to **5d**. [c] Isolated as the methyl ester following reaction with $TMSCHN_2$.



Scheme 3. Ligands examined in the asymmetric lithiation and methylation of thioamide **4**.

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Table 2: Effect of ligand and solvent on asymmetric lithiation and methylation of thioamide **4**.

Entry[a]	Ligand	Solvent	e.r. **5h** *R*:*S*	Conversion [**5h**/**4**][b]
1	**6**	Et_2O	61:39	99:1
2	**6**	TBME	59:41	99:1
3	**6**	THF	54:46	99:1
4	**6**	hexane	72:28	99:1
5[c]	**6**	hexane	52:48	99:1
6[d]	**6**	hexane	60:40	99:1
7[e]	**6**	pentane	71:29	97[f]
8	**7**	hexane	46:54	97:3
9	**7**	Et_2O	–	0:100
10	**8**	hexane	47:53	95:5
11	**8**	Et_2O	37:63	78:22
12	**9**	hexane	62:38	99:1
13	**9**	Et_2O	80:20	96[f]
14[e]	**9**	Et_2O	78:22	99:1
15	**9**	TMBE	76:24	99:1

[a] *s*BuLi (1.2 equiv), ligand (1.2 equiv), unless otherwise indicated. [b] by GC-MS, unless otherwise indicated. [c] 2.5 equivalents of **6** used. [d] *s*BuLi (4 equiv), **6** (4 equiv). [e] −100 °C. [f] Yield of isolated **5h**.

was found to be opposite to that previously observed with *s*BuLi/**6** using *N*-Boc-pyrrolidine as the substrate.[17] A study of the effect of solvent on the enantiomeric ratio found little change when *tert*-butyl methyl ether was used, a slight lowering in tetrahydrofuran, and an improvement to 72:28 in hexane (Table 2, entries 2–4). In hexane, increasing the proportion of (−)-sparteine (**6**) relative to *s*BuLi, or the number of equivalents of *s*BuLi/**6**, led to lower enantiomeric ratios (Table 2, entries 5 and 6), whereas conducting the reaction at −100 °C (in pentane) led to a similar result (**5h** isolated in 97% yield) to that initially observed in hexane (Table 2, entry 7). Proline-based ligands **7** and **8** were less effective than sparteine (Table 2, entries 8–11).[19] Alexakis and co-workers originally introduced *trans*-cyclohexane-1,2-diamines, such as **9** (now commercially available),[20] as ligands for the enantioselective addition of methyllithium to imines, in which the different substituents on each nitrogen atom allowed both heteroatoms to become stereocenters when chelated to the metal;[21] more recently, this diamine has been shown to induce asymmetric α lithiation of *N*-Boc-pyrrolidine with high efficiency, comparable to that obtained with (−)-sparteine (**6**).[22] When thioamide **4** was used as the substrate, although ligand **9** (in hexane) gave a lower e.r. value (Table 2, entry 12) compared to (−)-sparteine (**6**) (Table 2, entry 4), ligand **9** was found to be superior in ethereal solvents (up to 80:20 e.r. in diethyl ether at −78 °C, 96% yield of **5h**; Table 2, entries 13–15).

In summary, we report a method for the α incorporation of electrophiles onto azetidine, in which the rarely studied *N*-thiopivaloyl group[15,23] plays a crucial role. The origins of its effectiveness (compared with the more typical N-activating substituents examined above) are not known, but may result from a combination of α-position activation and a reduced/absent propensity for attack of the base at the thiocarbonyl functionality.[24] This method tolerates a variety of different electrophiles, and affords products in good diastereoselectivities; indeed, the scope is arguably better than for the well-studied *N*-Boc-pyrrolidine system. Furthermore, subsequent high-yielding removal of the *N*-thiopivaloyl group has been demonstrated. To the best of our knowledge, this chemistry also provides the first example of enantioselective electrophilic substitution on a four-membered ring.[25] It is tempting to speculate that, as with the *N*-Boc-pyrrolidine and piperidine systems,[2b] a ternary pre-lithiation complex involving the azetidine, organolithium and (chiral) ligand species facilitates the proton removal (equatorial, from a puckered azetidine conformation) to give a configurationally stable dipole-stabilized α-lithiated azetidine that undergoes methylation with retention of stereochemistry ($S_E2$ret). However, reversal of the major enantiomer compared with these other systems means that such speculation must be treated with caution at this stage and awaits clarification through mechanistic studies. Nevertheless, the promising levels of asymmetric induction, which were obtained using a ligand that is commercially available as either enantiomer and which has scope for structural variation (unlike sparteine), suggests this and related systems will provide fertile ground for future investigations.

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Keywords: asymmetric synthesis · azetidines · electrophilic substitution · lithiation · synthetic methods

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