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Amine Protection/α-Activation with the *tert*-Butoxythiocarbonyl Group: Application to Azetidine Lithiation−Electrophilic Substitution

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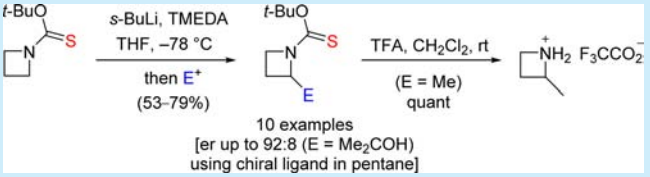
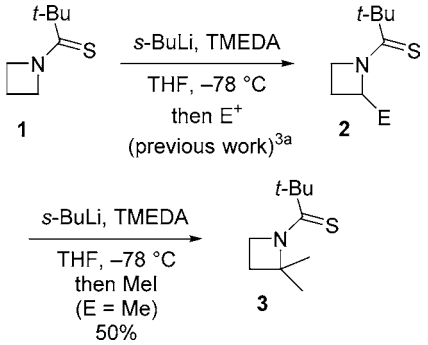
Supporting Information

ABSTRACT: *tert*-Butoxythiocarbonyl (Botc), the long-neglected thiocarbonyl analogue of Boc, facilitates (unlike its alkoxycarbonyl cousin) α-lithiation and electrophile incorporation on *N*-Botc-azetidine. *N,N,N′,N′-endo,endo*-Tetramethyl-2,5-diaminonorbornane proved optimal as a chiral ligand, generating adducts with er up to 92:8. Facile deprotection, under conditions that left the corresponding *N*-Boc systems intact, was achieved using either TFA or via thermolysis in ethanol.



An important strategy for the elaboration of amines is reaction of an α-C−H bond of a suitably *N*-protected/activated amine, with a number of methods applicable to saturated azacycles.[1] Azetidines are found in drug leads and bioactive natural products and are attracting increasing research interest.[2] In 2010, we reported a way to prepare substituted azetidines by lithiation−electrophile trapping at an α-methylene group (**1** → **2**) (Scheme 1), in which the rarely used *N*-thiopivaoylazetidines

Scheme 1. α-Lithiation−Electrophile Trapping of *N*-Thiopivaoylazetidines



thiopivaloyl group was effective (compared with the known pool of potential *N*-substituents such as Boc).[3] However, the *N*-thiopivaloyl group requires harsh conditions for its removal [MeLi (5 equiv), THF, 0 °C, 5 h]. In addition, we have subsequently found that the thiopivaloyl group unusually directs lithiation to an already substituted and unactivated 2-position (**2** → **3**) (Scheme 1),[4,5] indicating that the corresponding 2,4-disubstituted azetidines could not be accessed by this approach.

To address the above limitations, we considered using the *tert*-butoxythiocarbonyl (*t*-BuOC═S = Botc) group, on the basis that the retained thiocarbonyl group might still facilitate efficient azetidine α-lithiation[6] but the presence of the *tert*-butoxy group should allow for mild deprotection. Additionally, the oxygen "spacer" might allow access to a rotamer that could direct lithiation to the 4-position.[7] The present paper reports our promising results on this topic.

Four years after introducing the now ubiquitously used Boc group as protection for nitrogen, Carpino in 1961 suggested the *tert*-butoxythiocarbonyl group as a more acid-labile variant.[8] However, the latter has not been further examined in this context,[9] which may be due to a combination of perceived instability together with the originally highlighted limitation of accessibility solely from an isothiocyanate and *t*-BuOH.[10] The readily available tertiary alkyl xanthate ester **4**[11] was viewed as a potentially attractive reagent for one-step *tert*-butoxythiocarbonyl transfer to an amine. However, while the reaction of primary and secondary alkyl xanthate esters with amines (including azetidine) is an effective way to make *O*-alkyl thiocarbamates,[12] tertiary alkyl xanthate esters such as **4** are reported to give dithiocarbamates.[13] Notwithstanding this latter report, we found that xanthate ester **4** (1.1 equiv) reacted with azetidine to efficiently give the desired *tert*-butoxythiocarbonyl (Botc)-protected azetidine **5** (88%) (Scheme 2).[14]

As anticipated, *N*-Botc-azetidine **5** underwent facile deprotection under acidic conditions (Scheme 2) with no ring-opening being observed. Greater acid lability of *N*-Botc compared to *N*-Boc is illustrated by addition of TFA to a 1:1 mixture of **5** and *N*-Boc-azetidine, resulting in a ∼1:1 mixture of **6b** and unreacted *N*-Boc-azetidine.[15,16] The *N*-Botc-group could also be preferentially eliminated under thermal[17] conditions (EtOH, reflux, 12 h) (Scheme 3).

Significantly, Botc protection proved compatible with α-lithiation−electrophile trapping under similar conditions to those used previously with *N*-thiopivaloylazetidine **1** to give a

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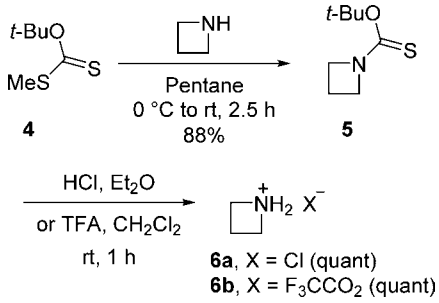
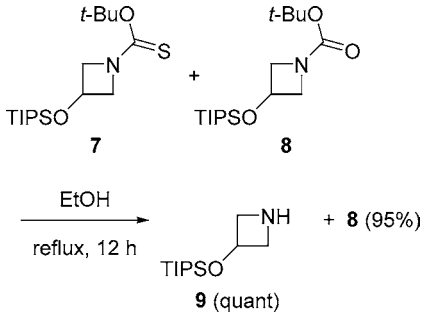
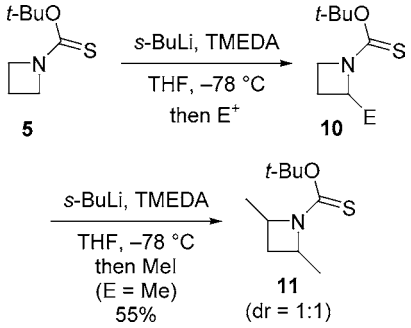
Scheme 2. Preparation and Deprotection of *N*-Botc-azetidine 5



Scheme 3. Selective *N*-Botc Deprotection



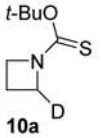
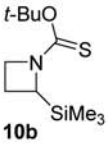
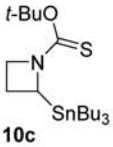
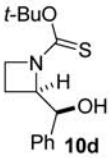
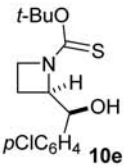
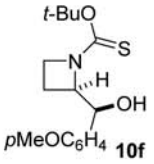
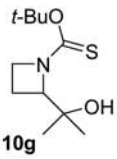
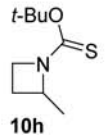
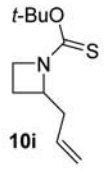
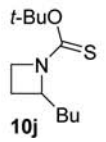
Scheme 4. α-Lithiation–Electrophile Trapping of *N*-Botc-azetidines



range of α-substituted *N*-Botc-azetidines **10** (Scheme 4, Table 1). Silylation, stannylation, and reaction with aromatic aldehydes all proved viable, with only a slight reduction in yield seen for the more electron-rich *p*-anisaldehyde (Table 1, entry 6). A potentially enolizable ketone was also seen to react satisfactorily (Table 1, entry 7). Good alkylation reactivity, similar to that previously seen with *N*-thiopivaloylazetidine **1**, was observed (Table 1, entries 8–10); this is notable because alkylation of dipole-stabilized organolithiums can be problematic due to SET processes.[18] Deprotection of an α-substituted *N*-Botc-azetidine could also be achieved with TFA, in quantitative yield from **10h**.[15] Also noteworthy is that a second methylation of monomethylated *N*-Botc-azetidine **10h** occurred exclusively at the 4-position to give *N*-Botc-2,4-dimethylazetidine **11** (55%, 93% brsm),[4] albeit with no diastereoselectivity (Scheme 4).

Previously with *N*-thiopivaloylazetidine **1**, a single example of enantiocontrolled introduction of an electrophile had been demonstrated: methylation in er up to 80:20 using a *trans*-cyclohexane-1,2-diamine **12** (Figure 1) in Et_2O (using (−)-sparteine **13** gave er up to 72:28 in hexane).[3a] Initial

Table 1. Scope of Electrophile Incorporation into *N*-Botc-azetidine 5

entry	E^+	10	yield
1	CD_3OD	 **10a**	90% (95% D)[a]
2	Me_3SiCl	 **10b**	76%
3	Bu_3SnCl	 **10c**	75%
4	PhCHO	 **10d**	74%[b]
5	$pClC_6H_4CHO$	 **10e**	69%[b]
6	$pMeOC_6H_4CHO$	 **10f**	57%[b]
7	Me_2CO	 **10g**	65%
8	MeI	 **10h**	79%
9	allylBr	 **10i**	53%
10	BuBr	 **10j**	77%

[a]By mass spectrometry. [b]dr = 70:30, major (*R**,*S**) diastereomer shown.[15]

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studies on enantioselective methylation of *N*-Botc-azetidine **5** using 1,2-diamine **12** or (−)-sparteine **13** (or structurally related 1,2-diamines or bispidines) in either Et_2O or hexane were disappointing, giving er's less than 60:40.[15] Alexakis and co-workers recently examined 2,5-diaminonorbornanes (DIANANEs, readily available in either enantiomeric form) in several asymmetric transformations involving organolithiums, including enantioselective deprotonation−silylation of *N*-Boc-pyrrolidine using *s*-BuLi in Et_2O and where the maximum er (85:15) was observed with tetramethyl DIANANE **14**.[19] Use of this latter ligand for methylation of *N*-Botc-azetidine **5** proved more encouraging, giving azetidine (*R*)-**10h** in 73% yield and er = 69:31 in hexane at −78 °C (64% yield and er = 56:44 in Et_2O).

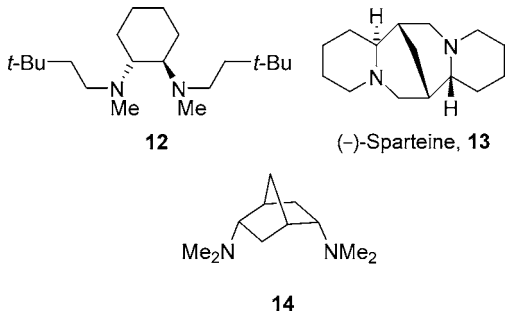
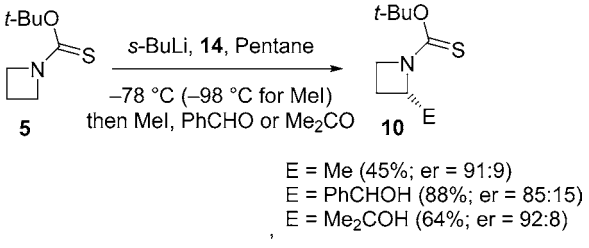


Figure 1. Ligands examined in asymmetric lithiation.

As higher alkyl-substituted DIANANEs were found not to promote formation of *N*-Botc-2-methylazetidine **10h**,[15] a more detailed examination of lithiation and methylation with tetramethyl DIANANE **14** in hydrocarbon solvent was undertaken. Deuterium-trapping experiments using CD_3OD allowed the extent of lithiation and chemical stability of Li−**5** to be determined. In the absence of a ligand, 15% D incorporation was observed after 1 h at −78 °C, whereas no reaction was observed at −98 °C. In the presence of ligand **14**, lithiation was essentially complete after 5 min at −78 °C (90% D), after 1 h at −98 °C 77% D incorporation was observed which rose to 95% after 3 h; quantitative mass recovery of **5**/**10a** was obtained in each case, indicating good chemical stability of Li−**5** under these conditions. The enantioselectivity of the reaction was found to be dependent on the durations of lithiation and methylation and the temperatures at which both of these steps were carried out.[15] Lithiation and reaction with MeI both for 1 h at −98 °C proved optimal for methylation in terms of er (er = 91:9; 45% yield, 83% based on recovered **5**). Asymmetric α-substitution of *N*-Botc-azetidine **5** was not restricted to methylation, as demonstrated by reaction with benzaldehyde and acetone in er up to 92:8 (Scheme 5).

Scheme 5. Asymmetric α-Lithiation−Electrophile Trapping of *N*-Botc-azetidine 5



As originally envisaged by Carpino more than half a century ago,[8] the above studies show a promising profile for the *tert*-butoxythiocarbonyl (Botc) group as an amine protecting group. The Botc group can be efficiently introduced onto a secondary amine from the corresponding xanthate ester, despite literature data indicating that only the corresponding dithiocarbamate would be formed.[13] In the context of azetidine elaboration, Botc facilitates lithiation−electrophile trapping, which to the best of our knowledge is the first use of *O*-alkyl thiocarbamate functionality enabling substitution α- to nitrogen.[6] Compared to thiopivaloyl, Botc can be removed under mild acid or thermal conditions and selectively in the presence of *N*-Boc. The latter observations indicate that Botc should find wider synthetic utility. Furthermore, Botc shows a different reactivity profile to thiopivaloyl with a 2-substituted azetidine, allowing access to 2,4-disubstitution. The Botc group gives the best levels of enantioselectivity in azetidine α-substitution to date (er up to 92:8), showing electrophile scope beyond the originally demonstrated methylation. The present work also provides the highest levels of asymmetric induction observed thus far in an organolithium-based transformation with a DIANANE ligand, providing encouragement to investigate both this ligand class further as well as the Botc group to facilitate other enantioselective processes.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(4) The origin of this regioselectivity is currently under investigation.
(5) *N*-Boc-2-phenylazetidine has recently been shown to undergo benzylic lithiation and in situ electrophile trapping in modest yields (32−38%); external electrophiles failed: Degennaro, L.; Zenzola, M.; Trinchera, P.; Carroccia, L.; Giovine, A.; Romanazzi, G.; Falcicchio, A.; Luisi, R. *Chem. Commun.* **2014**, *50*, 1698−1700.
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(7) For lithiation−electrophile trapping at the 5-position of *N*-Boc-2-methylpyrrolidine, see: Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109−1117.
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(13) Barrett, G. C.; Martins, C. M. O. A. *J. Chem. Soc., Chem. Commun.* **1972**, 638−639.
(14) Similar, but slightly lower yields of *N*-Botc-azetidine **5** (73−87%) were obtained with CH_2Cl_2 as solvent or under solvent free conditions; use of H_2O or 50% aq dioxane gave more variable results due to poor solubility. Similar observations were made for *N*-Botc-pyrrolidine and *N*-Botc-piperidine; see also ref 15.
(15) See the Supporting Information for details.
(16) A similar result was obtained with a 1:1 mixture of *N*-Botc-pyrrolidine and *N*-Boc-pyrrolidine; see also ref 15.
(17) Newman, M. S.; Hetzel, F. W. *J. Org. Chem.* **1969**, *34*, 3604−3606.
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