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Selective cleavage of 3,5-bis-(trifluoromethyl)benzylcarbamate by SmI_2–Et_3N–H_2O†

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A novel electron poor protection group for amines has been developed. It undergoes rapid cleavage by SmI_2–Et_3N–H_2O and its orthogonality towards the regular benzyl carbamate group (CBz) under reductive or transfer hydrogenolytic conditions is reported.

Protecting groups are powerful tools for the synthesis of multifunctional compounds to temporarily mask sites of similar reactivity in targets such as oligosaccharides and peptides.[1] Although it is desirable to minimize their use due to the low atom economy and increased number of steps, the versatility offered by this technique is still unprecedented.[2] Herein we present a new protection group for amines that exploits the exceptionally high reactivity of electron deficient carbamates towards the powerful reducing agent SmI_2–Et_3N–H_2O (Fig. 1).

Protecting groups should ideally meet several criteria: (i) easy to introduce and high yielding, (ii) stable under a wide range of reaction conditions and (iii) use of mild conditions for its removal allowing for deprotection without interfering with other functionalities present. If the protecting group in addition is retained during the removal of alternative protecting groups it is orthogonal to these, which is a highly desirable property.[3] The amine plays a special role in organic synthesis as it is a functional group present in almost all compounds of biological relevance, but its high polarity and basicity frequently pose problems during multistep synthesis of these compounds. Therefore, a wide range of protecting groups for amines have been developed that can be removed under for instance acidic, reductive and oxidative conditions respectively.

The reductive chemistry of divalent samarium has been the subject of intense research over the last 30 years, and its reactivity can be successfully fine-tuned to achieve the desired transformations.[4] We have previously developed highly efficient protocols for unmasking both allyl protected alcohols[5] and tosyl protected amines and alcohols[6] using SmI_2–Et_3N–H_2O. During our studies of the benzylic deoxygenation using the same reagent combination,[7] we discovered that the trifluoromethyl substituted benzyl alcohols underwent this reaction very fast. We have now developed a new variety of the carbonylbenzyloxy (CBz) group that takes advantage of this accelerating effect, namely 3,5-bis-(trifluoromethyl)-benzyloxycarbonyl (CBTFB). This new protecting group is resistant towards acids, hydrogenation[8] and oxidation, but highly sensitive towards the reductive reagent SmI_2–Et_3N–H_2O, which indicates that it is also sensitive to single electron transfer. We believe that protecting groups that are resistant to such diverse conditions are rare and thus valuable additions to the available protection strategies that exist for amines.

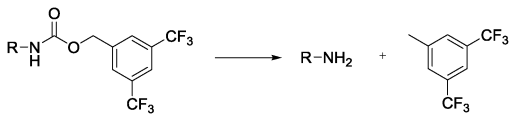
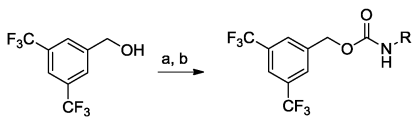


Fig. 1 A highly electronegative benzyloxy carbamate (CBTFB) is very efficient as a protecting group for amines.

The introduction of 3,5-bis-(trifluoromethyl)benzylcarbamate is achieved in very high yields after a simple two-step sequence starting from the commercially available 3,5-bis-(trifluoromethyl)benzyl alcohol (Scheme 1). The intermediate chloroformate could also be prepared in larger quantities and stored at 4 °C for weeks with no detection of reduced reactivity. The formed derivatives are generally very easy to handle and obtained as solids in all cases. In addition, the high lipophilicity of the CBTFB group gives desirable solubility properties in organic solvents.



Scheme 1 Protection of amine with a CBTFB group. (a) $COCl_2$, THF, rt. (b) Amine, $NaHCO_3$, acetone–water, rt.

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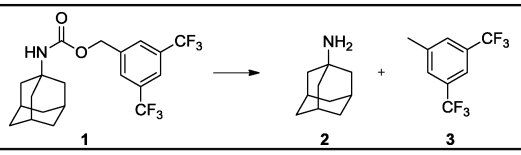
† Electronic supplementary information (ESI) available: NMR data of protected compounds. See DOI: 10.1039/c3cc41642a

Table 1 Evaluation of the effect of various reducing agents on CBTFB protected amine



1 2 3

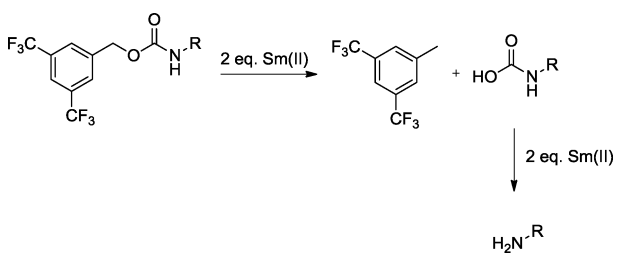
Entry	Reagent[a]	Time	Yield
1	SmI_2	24 h	n/r
2	SmI_2–H_2O (50 equiv.)	24 h	15%
3	SmI_2–Et_3N–H_2O	5 min	>95%
4	SmI_2–TPPA[b]	24 h	>95%
5	SmI_2–TPPA–MeOH	5 min	>95%

[a] See the Experimental section for details regarding the exact reaction conditions. [b] Tripyrrolidinophosphoric acid triamide (TPPA).

To evaluate the reaction conditions for the deprotection we chose the adamantyl derivative **1** as a model substance. We exposed **1** to SmI_2 (entry 1, Table 1), but no reaction could be detected over 24 hours. Addition of common co-solvents however proved more successful (entries 2–5, Table 1). The additive combination previously developed by our group (entry 3, Table 1) outperformed the other reagents in terms of the reaction rate, ease of work-up and yield. In theory, the cleavage reaction demands four electrons in total in order to break the two bonds. Thus addition of 4 equivalents of SmI_2 with Et_3N (8 equiv.) and water (12 equiv.) was found to give full conversion of the free amine (**2**) in less than 5 min. Addition of less than 4 equivalents Sm(II) gave incomplete conversion to **2** and **3**. Analysis of the post-reaction mixture using 2 equivalents of Sm(II) revealed no intermediates. The fact that more than 2 equivalents of Sm(II) are consumed suggests that products from the cleavage reacts faster with Sm(II) than with the CBTFB-group (Scheme 2).

To gain deeper understanding of the reactivity of the CBTFB group we performed competitive experiments with the CBz protected adamantylamine. Thus, a solution containing both **1** and *N*-CBz adamantylamine in equimolar amounts was added to an excess of SmI_2–Et_3N–H_2O. After completion of the reaction the reaction mixture was analyzed and it was found that the CBTFB protected amine was fully consumed, while the CBz protected adamantylamine was left intact. Furthermore, we followed the reaction over time and it could be seen that the decay of **1** was rapid at room temperature and no carbamate could be detected after 100 s.

Intrigued by this, we devised an experiment utilizing a standard cleavage protocol for the CBz group,[9] *i.e.* hydrogenolysis with Pd–C and Et_3N–formic acid. The hydride donor



Scheme 2 A 4-electron reduction of the carbamate bond with SmI_2, R_3N and H_2O yields bis-CF_3–toluene and the free amine.

Table 2 Stability tests performed on **1**

Entry	Conditions[a]	Reaction
1	10% TFA in DCM, rt	Stable 24 h
2	CAN–DMF, rt	Stable 24 h
3	Piperidine–DMF	Stable 24 h
4	Ammonia in MeOH (1.0 M)	Stable 24 h
5	K_2CO_3–MeOH	Stable 24 h
6	HBr in HAc	Degraded
7	20% KOH in MeOH	Degraded

[a] See the Experimental section for details regarding the exact reaction conditions (ESI).

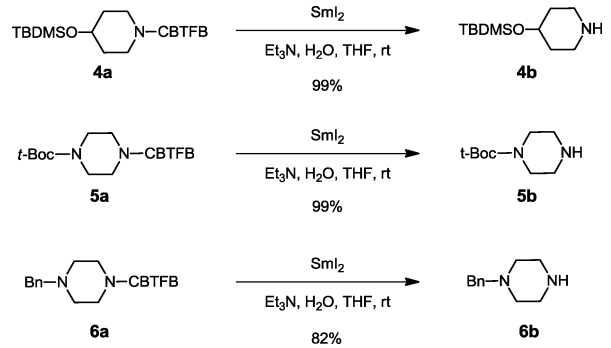
(formic acid) was added in portions, and samples were subsequently analyzed to monitor the concentration of the amine over time. *This time, a reversal in the selectivity between the protecting groups was noted.* While the CBz protected adamantylamine was fully deprotected, the CBTFB protected adamantylamine was left intact. This also lead to the conclusion that this protecting group is compatible with isolated double bonds as SmI_2–Et_3N–H_2O has proven unreactive towards such functionalities, a feature that frequently restricts the use of transition metal catalyzed deprotection protocols.

To further evaluate the synthetic potential of this protecting group, we subjected the model substance to a set of conditions used for the deprotection of other common protecting groups for amines and alcohols (Table 2). It was found that **1** was stable in 10% TFA in DCM (entry 1, Table 2), the reagent of choice for cleaving *t*-Boc groups,[10] over 24 hours. Neither did the addition of ceric(IV)ammonium nitrate (entry 2) or piperidine (entry 3), reagents used to cleave PMB[11] and Fmoc[12] groups, respectively, result in a cleavage reaction. Ammonia in methanol (entry 4) or potassium carbonate (entry 5), frequently used to deprotect trifluoroacetamides,[13] also proved unreactive during 24 h exposure. More forcing conditions, *i.e.* strong reductive/hydrolytic conditions (HBr in HAc – known to cleave tosylamides)[14] and strongly alkaline conditions (20% KOH in MeOH), degraded the carbamate within 10 minutes.

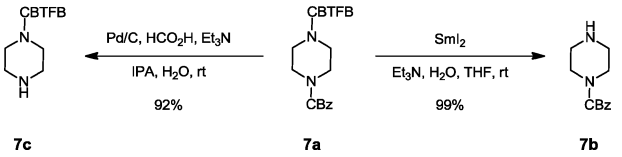
The above results provide evidence that this protecting group is orthogonal to many of the common groups and yet it is easily deprotected using SmI_2–Et_3N–H_2O. The resistance towards hydrogenolysis renders it complementary to the allyloxycarbonyl (Aloc)[15] and trichloroethyloxycarbonyl (Troc)[16] groups, which show similar reactivity (*i.e.* acid stable and slightly labile towards bases) but these are not stable towards hydrogenolysis conditions. Altogether, the features of this novel protecting group are markedly different from common protecting groups for amines and offer a new "selectivity window" for organic synthesis of multifunctional substrates previously unavailable.

In order to explore the scope of the deprotection in the presence of other protecting groups, we prepared a set of bis-protected compounds and subjected them to SmI_2–Et_3N–H_2O. From the result presented in Scheme 3, it can be concluded that the CBTFB group can be deprotected in excellent isolated yield in the presence of various commonly used protecting groups such as TBDMS (**4a**), *t*-Boc (**5a**), and benzyl (**6a**).

We were also interested in applying the results from the competing experiments, *i.e.* having both a CBz and a CBTFB



Scheme 3 Deprotection reactions using 4 equivalents of SmI_2 with triethylamine and water.



Scheme 4 Deprotection reaction of **7a** using either 4 equivalents of SmI_2 with triethylamine and water to yield **7b** or Pd–C to yield **7c**.

group within the same molecule (Scheme 4). To our delight the CBTFB group was cleanly deprotected leaving the mono CBz protected amine (**7b**) in exceptional yields. **7a** was also subjected to transfer hydrogenolysis conditions and again we found very high yield of the mono deprotected amine (**7c**), this time with the CBTFB group intact (Scheme 4).

Protection of thiols is another highly important transformation in for instance protein synthesis.[17] However, sulfur is not easy to protect efficiently and hence new methodologies are always welcome additions to the available groups. We evaluated CBTFB as a thiol protecting group and found that the deprotection was successful using SmI_2–Et_3N–H_2O, and the free thiol could be isolated in excellent yield. Furthermore, it was stable under hydrogenolysis conditions (Pd–C with formic acid) but considerably more sensitive to the corresponding carbamate base, which was rapidly cleaved by both potassium hydroxide and potassium carbonate in methanol. It was also sensitive to piperidine and ammonia yielding the free thiol and the CBTFB derivative of the amine. It was however stable to 10% TFA and CAN for long periods of time.

Other single electron transfer reagents were also assayed in the reductive cleavage of the carbamate bond. The deprotection of the carbamate with Mg–MeOH[18] was observed to proceed very slowly and it also gave rise to extensive defluorination of both the CBTFB group and the resulting 3,5-bis(trifluoromethyl)toluene that arises from the cleavage reaction.[19] Zinc and ammonium chloride[19] were also explored for removal of the electron poor carbamate but we observed no cleavage. This indicates that reduction effected by this reagent is possible in the presence of the CBTFB group.

To conclude, a protecting group for amines and thiols has been developed that can be selectively cleaved under mild SET conditions. In this respect, this group has a unique property that is not shared by any of the existing carbamate protecting groups (Troc, Aloc, Boc, *etc.*). Although other protective groups can certainly be removed using SET reagents, they frequently require very harsh reaction conditions. The electron deficient benzyl carbamate CBTFB is a promising new protecting group for amines that exploits the exceptionally high sensitivity of electron deficient carbamates towards reducing agents and in particular SmI_2–amine–water. The CBTFB protecting group is easy to introduce and is stable towards most reaction conditions but very sensitive towards reductive conditions, *i.e.* SmI_2–H_2O–amine-mediated, while it is practically inert towards hydrogenation. We believe that the introduction of this unique protecting group is important as it is cleaved under very specific reaction conditions and can potentially be used under many different reaction conditions. Thus it fulfills all the criteria for protecting groups outlined above and holds promise as an important addition to the existing strategies for amine and thiol protection. We are currently aiming to develop the chemistry of this protecting group and to further test the functional group tolerance associated with its removal as well as its use in amino glycoside and peptide synthesis.

Notes and references

1 (*a*) P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 2007; (*b*) P. J. Kocienski, *Protecting Groups*, Georg Thieme Verlag, Stuttgart and New York, 1994.
2 P. S. Baran, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404–408.
3 (*a*) G. Barany and R. B. Merrifield, *J. Am. Chem. Soc.*, 1977, **99**, 7363–7365; (*b*) G. Barany and F. Albericio, *J. Am. Chem. Soc.*, 1985, **107**, 4936–4942; (*c*) M. Schelhaas and H. Waldmann, *Angew. Chem., Int. Ed.*, 1996, **35**, 2056–2083.
4 (*a*) D. J. Procter, R. A. Flowers and T. Skrydstrup, in *Organic synthesis using samarium diiodide: a practical guide*, Royal Society of Chemistry Publishing, U.K., 2010; (*b*) G. A. Molander, *Org. React.*, 1994, **46**, 211–367; (*c*) K. Urtimoto and S. Matsubara, *Organomet. News*, 1995, 38–40; (*d*) G. A. Molander and C. R. Harris, *Tetrahedron*, 1998, **54**, 3321–3354; (*e*) H. B. Kagan and J.-L. Namy, *Top. Organomet. Chem.*, 1999, **2**, 155–198; (*f*) A. Krief and A.-M. Laval, *Chem. Rev.*, 1999, **99**, 745–777; (*g*) P. G. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727–2751; (*h*) H. B. Kagan, *Tetrahedron*, 2003, **59**, 10351–10372; (*i*) A. Dahlen and G. Hilmersson, *Eur. J. Inorg. Chem.*, 2004, 3393–3403; (*j*) R. A. Flowers, *Synlett*, 2008, 1427–1439; (*k*) K. C. Nicolaou, P. E. Shelby and S. C. Jason, *Angew. Chem., Int. Ed.*, 2009, **48**, 7140–7165; (*l*) K. A. Choquette, D. V. Sadasivam and R. A. Flowers, II, *J. Am. Chem. Soc.*, 2010, **132**, 17396–17398.
5 A. Dahlen, A. Sundgren, M. Lahmann, S. Oscarson and G. Hilmersson, *Org. Lett.*, 2003, **5**, 4085–4088.
6 T. Ankner and G. Hilmersson, *Org. Lett.*, 2009, **11**, 503–506.
7 T. Ankner and G. Hilmersson, *Tetrahedron*, 2009, **65**, 10856–10862.
8 The resistance towards hydrogenolysis of 4-trifluoromethylbenzyl carbamates has been noted before. See E. A. Papageorgiou, M. J. Gaunt, J. Yu and J. B. Spencer, *Org. Lett.*, 2000, **2**, 1049–1051.
9 B. Elamin, G. M. Anantharamaiah, G. P. Royer and G. E. Means, *J. Org. Chem.*, 1979, **44**, 3442–3444.
10 A. S. Ripka, R. S. Bohacek and D. H. Rich, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 357–360.
11 S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3765–3774.
12 L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 1972, **37**, 3404–3409.
13 M. Imazawa and F. Eckstein, *J. Org. Chem.*, 1979, **44**, 2039–2041.
14 D. A. Alonso and P. G. Andersson, *J. Org. Chem.*, 1998, **63**, 9455–9461.
15 F. Guibe, *Tetrahedron*, 1997, **53**, 13509–13556.
16 T. B. Windholz and D. B. Johnston, *Tetrahedron Lett.*, 1967, 2555.
17 F. Cavelier, J. Daunis and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1990, 210–225.
18 J. A. Profitt, D. S. Watt and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 127–128.
19 This is probably because of the fact that the reaction takes place at the surface of the magnesium metal, lowering the selectivity due to transport phenomena.