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The fate of the *tert*-butylsulfinyl auxiliary after acid-promoted cleavage—a method for recycling *t*-BuSONH$_2$

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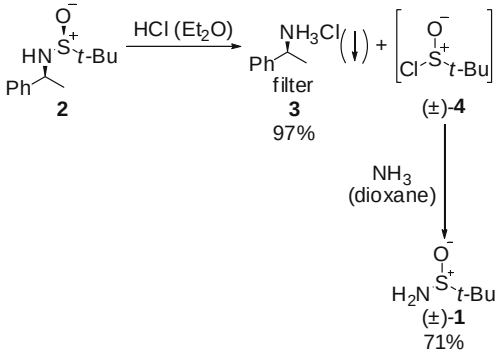
ABSTRACT

Ellman's chiral auxiliary is converted into *tert*-butylsulfinyl chloride on sulfinamide deprotection with HCl and can be recovered in high yield upon treatment with ammonia. The enantiopure auxiliary can be obtained by trapping the sulfinyl chloride with a chiral alcohol followed by treatment of the resulting sulfinate ester with LiNH$_2$.

Amongst the chiral auxiliaries for the preparation of enantiopure amines and aziridines, Ellman's *t*-butyl-sulfinamide group **1** stands out.[1] It provides very high enantioselectivities in a spectrum of different classes of reactions and with a broad range of substrates.[2] The routinely high selectivity observed, coupled with its ease of introduction and removal has made it the auxiliary of choice for chiral amine synthesis. We had occasion to employ the *tert*-butylsulfinyl group in a short synthesis of balanol[3] but we were intrigued by the fate of the auxiliary during the acid (HCl) promoted deprotection. One might expect, based upon analogy with Boc and *tert*-BuSO$_2$ groups,[4] that the auxiliary would decompose to innocuous by-products, for example, isobutylene and 'SO'. However, whilst Boc and *tert*-BuSO$_2$ groups readily liberate the stable gases CO_2 and SO_2, 'SO' is extremely unstable and so should not form easily.[5] We therefore reasoned that the auxiliary may still be intact following deprotection with HCl and could therefore be present as the sulfinyl chloride.[6] To test this hypothesis enantiopure sulfinamide **2** was treated with HCl in Et$_2$O and following removal of the amine salt **3** by filtration the filtrate was treated with concentrated NH$_3$ in dioxane (Scheme 1). To our delight the parent *tert*-butylsulfinamide was regenerated and isolated in good yield indicating that our hypothesis was indeed correct.

Whilst the *tert*-butylsulfinamide was isolated in good yield, it was found to be racemic. This was not surprising as it is known



Scheme 1. Recovery of (±)-**1** after cleavage of the auxiliary.

that HCl racemizes sulfoxides and sulfinate esters through formation of trigonal bipyramidal intermediates.[7] While it is clearly useful to be able to reisolate the parent *tert*-butylsulfinamide, it would be even more useful if it could be obtained in high enantiopurity. Thus, a number of experiments were conducted in an attempt to preserve the chirality of the sulfinyl group through a single operation, but without success.[8] We therefore considered an alternative strategy involving a dynamic kinetic resolution since it was known that racemic sulfinyl chlorides can react with chiral alcohols with good levels of diastereoselectivity.[9–11] We therefore screened the reaction of *tert*-butylsulfinyl chloride with several cheap chiral

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alcohols (Fig. 1) in the presence of different bases (Table 1 shows selected examples). From this study *N*-methylephedrine (NME) emerged as the optimum alcohol giving the corresponding sulfinate ester with high levels of diastereocontrol (Table 1, entry 9). Under these conditions, the sulfinate ester could be isolated in 60% yield as an 11:1 mixture of diastereomers. A small amount of thiolsulfonate[12] **9** (~8%) was also obtained accounting, in part, for the moderate yield of the required sulfinate ester.

Having established suitable conditions for reaction of the *tert*-butylsulfinyl chloride, we next sought conditions for deprotection of the sulfinamide *with* capture of the auxiliary.[13] On treatment of a solution of sulfinamide **2** in Et_2O with ethereal HCl (2.1 equiv) the ammonium salt **3** precipitated in excellent yield. Our optimization efforts focused on improving the yield and dr of the sulfinate ester. The filtrate was added to a flask containing **8** and base. Triethylamine proved to be the optimum base in terms of yield and dr (pyridine, DMAP and Hünig's base were all tested but gave <20% yield). It was found that the formation of **9** was suppressed by increasing the concentration so ultimately the second flask contained neat **8** in Et_3N. Under our optimized conditions (Scheme 2) we were able to isolate the sulfinate ester **10** in 58% yield as a single diastereomer after column chromatography. The ester was easily converted into the parent sulfinamide (*S*)-**1** in 84% yield by treatment with $LiNH_2/NH_3$,[14] thus demonstrating that enantiopure *tert*-butylsulfinamide can be recycled after use.

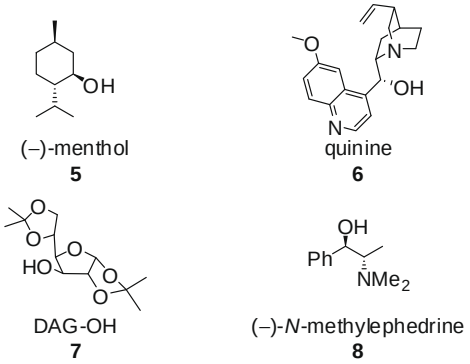
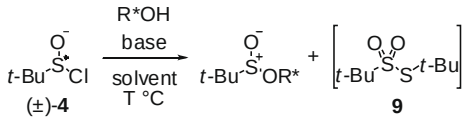


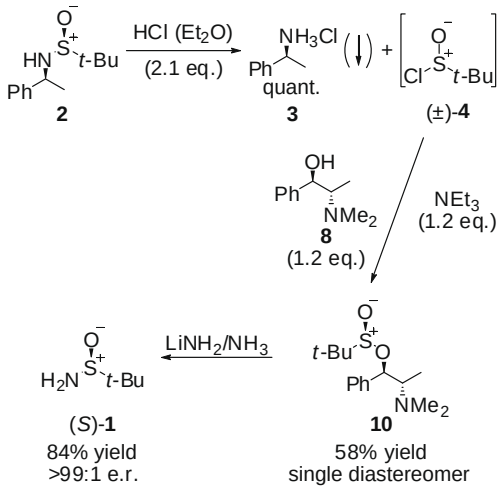
Figure 1. Alcohols screened for trapping *tert*-butyl-sulfinyl chloride (DAG–OH = diacetone-D-glucose).

Table 1
Screening of alcohols for recovery of sulfinate ester[a]



Entry	R*OH	Solvent	Base	*T* (°C)	dr[b]
1	**5**	CH_2Cl_2	Et_3N	−78	3:1
2	**5**	Toluene	iPr_2EtN	−78	3:1
3	**5**	1,4-Dioxane	iPr_2EtN	rt	3:1
4	**6**	1,4-Dioxane	Et_3N	rt	4:1
5	**7**	1,4-Dioxane	Et_3N + DMAP[c]	rt	3.5:1
6	**7**	Et_2O	Et_3N	−78	1:1
7	**7**	CH_2Cl_2	Et_3N + DMAP[c]	−78	2:1
8	**8**	1,4-Dioxane	Et_3N	rt	6:1
9	**8**	Et_2O	Et_3N[d]	rt	11:1

[a] 1 equiv R*OH, 1.2 equiv *t*-BuSOCl, 1.2 equiv base.
[b] Determined by ^1H NMR.
[c] 0.3 equiv DMAP.
[d] 2.5 equiv NEt_3.



Scheme 2. Recovery of enantiopure *tert*-butyl sulfinamide following removal of the auxiliary.

In conclusion, we have demonstrated that the *tert*-butylsulfinyl group is not destroyed during deprotection of sulfinamides with HCl, but is in fact converted into (±)-*tert*-butylsulfinyl chloride, which can react with NH_3 to give the parent sulfinamide. This discovery has allowed the development of a method for the recovery of the chiral auxiliary in enantiopure form by initial treatment with *N*-methylephedrine followed by $LiNH_2/NH_3$. As the auxiliary is rather expensive both sets of transformations are likely to prove useful in the future. Perhaps of greater importance though, is simply the knowledge of the fate of the auxiliary upon deprotection. Its presence means that one has to be cautious in isolating the product amine from the reaction mixture. If it is simply treated with base, the free amine will react with the sulfinyl chloride and give back the sulfinamide suggesting that the deprotection has not been successful.[15] It is thus imperative that the ammonium salt is separated from the *tert*-butylsulfinyl chloride by-product prior to basification.

Note added in proof

The following papers were published after this paper was submitted: (a) M. Wakayama, J. A. Ellman *J. Org. Chem.*, **2009**, Articles ASAP; DOI: 10.1021/jo9001883. Recycling the *tert*-Butanesulfinyl Group in the Synthesis of Amines Using *tert*-Butanesulfinamide; (b) F. Ferreira, C. Botuha, F. Chemla, A. Pérez-Luna, *Chem. Soc. Rev.*, **2009**, advance article; DOI: 10.1039/b809772k; *tert*-Butanesulfinimines: structure, synthesis and synthetic applications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.020.

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