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A Stereospecific Synthesis of Chiral Cyclic Sulfinamides

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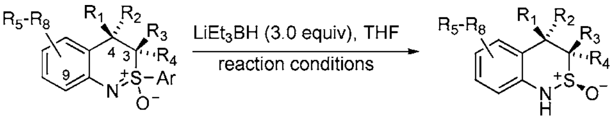
ABSTRACT



Treatment of racemic or enantiomerically pure 2,1-benzothiazines (cyclic sulfoximines) with lithium triethylborohydride results in clean loss of the *S*-aryl group with complete retention of configuration at sulfur to produce diastereomerically and/or enantiomerically pure cyclic sulfinamides in excellent yield.

Since the early 20th century the chemistry of sulfinamides has been of continuing interest.[1] Sulfinamides are valuable precursors for the synthesis of chiral amines and their derivatives,[2] aziridines,[3] sulfoximines and related species,[4] benzothiazines,[5] olefins, and ketones.[6] Sulfinamides also play pivotal roles in asymmetric synthesis as chiral auxiliary groups in the Diels−Alder reactions[7] and also as organocatalysts in the enantioselective reduction of ketimines.[8] More recently, a sulfinamide has been used as a P,S═O ligand in the asymmetric Pauson−Khand reaction.[9] A number of methods have been developed for the synthesis of sulfinamides from sulfinic acids,[10] sulfinates,[11] *N*-sulfinylamines,[12] thiosulfinates,[13] oxathiazolidine oxides,[14] sulfoximines,[15] benzothiazines,[16] and sulfonyl chlorides.[17]

Though remarkable progress has been made in the acyclic sulfinamide chemistry, the chemistry of cyclic sulfinamides remains less developed. Several approaches have been reported to access cyclic sulfinamides,[18] of which only two can access chiral cyclic sulfinamides.[18d,e] Both lack generality. We herein report a novel stereospecific synthesis of enantiopure cyclic sulfinamides by the dephenylation of chiral 2,1-benzothiazines.

In the course of a projected total synthesis of *seco*-pseudopteroxazole,[19] synthetic efforts were made to convert

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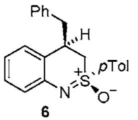
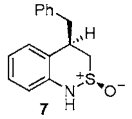
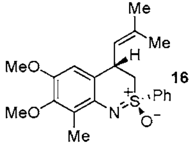
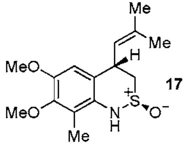
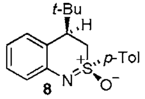
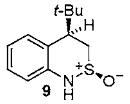
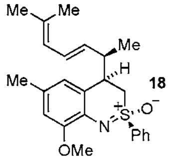
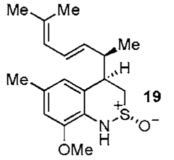
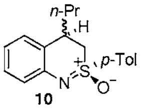
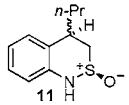
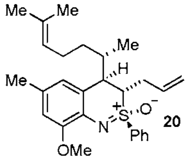
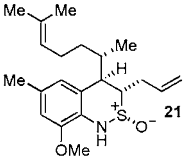
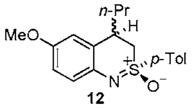
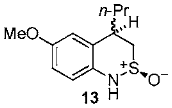
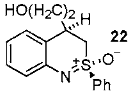
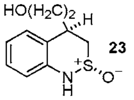
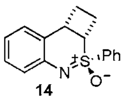
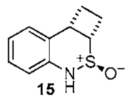
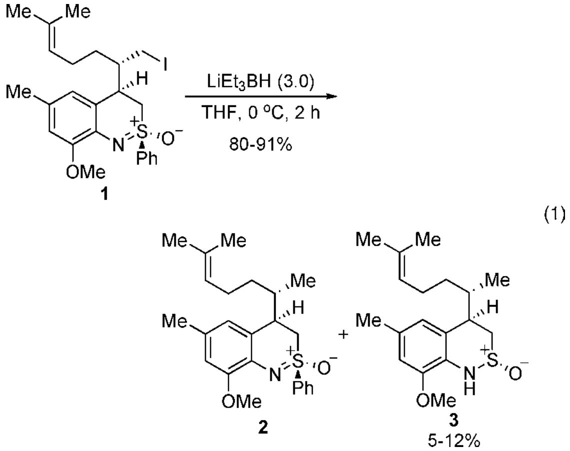
Table 1. Dephenylation of Benzothiazines

entry	benzothiazine[a,h]	sulfinamide[h]	Yield (%)[b]	entry	benzothiazine[a,h]	sulfinamide[h]	yield (%)[b]
1	 **6**	 **7**	99[c]	6	 **16**	 **17**	90[e]
2	 **8**	 **9**	96[c]	7	 **18**	 **19**	84[f]
3	 **10**	 **11**	90[c]	8	 **20**	 **21**	89[g]
4	 **12**	 **13**	70[c]	9	 **22**	 **23**	70[d]
5	 **14**	 **15**	59[d] (73 brsm)				

[a] Compounds **6**, **8**, **10**, and **12** were racemic. [b] Yields are for chromatographically purified materials. [c] Refluxed for 24 h. [d] Refluxed for 12 h. [e] Refluxed for 3 h. [f] Refluxed for 8 h. [g] Held for 12 h at room temperature. [h] Diastereomeric ratios determined by ^{1}H NMR of crude reaction mixtures: **10**, 1.6:1; **11**, 1.7:1; **12**, 1.3:1; **13**, 1.3:1; **20**, 8.1:1, **21**, 8.2:1.

iodide **1** into **2**, since the latter is expected to be key intermediate in the total synthesis. After extensive exploration, conditions utilizing 3.0 equiv of lithium triethylborohydride were adopted to afford **2** in 80−91% yield (eq 1). Despite an excellent yield of desired product, we did notice that a small amount of a side product was isolated in low yield. An ^{1}H NMR spectrum showed the absence of the *S*-phenyl group. The distinct deuterium exchangeable peak (6.86 ppm), combined with IR data (3252, 1082, 878, 829 cm^{-1}) suggested the presence of a sulfinamide functional group in the molecule. The structure was thus assigned as **3**.

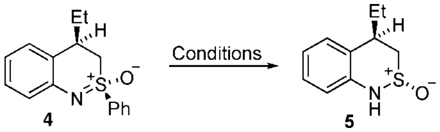


1 **2** **3** 5-12%

(1)

To confirm the intermediacy of **2** in this novel dephenylation reaction,[20] **2** was treated with 3.0 equiv of lithium triethylborohydride. After being stirred for 12 h at 0 °C and 6 h at room temperature, sulfinamide **3** was isolated in 57% yield, accompanied by 12% of recovered starting material.

Excited by these results, we synthesized enantiomerically pure **4** from readily available methyl 2-bromocinnamate.[21]



4 **5**

(2)

With **4** in hand, we set out to optimize the reaction conditions for dephenylation. A mixture containing **4** and **5** (0.46:1.0) was obtained after 24 h at room temperature when **4** was treated with 3.0 equiv of lithium triethylborohydride. When the reaction was refluxed for 6 h, **5** was isolated in 71% yield as a single diastereomer, whose structure was confirmed by X-ray analysis. Compound **4** was found to slowly decompose when stirred with LAH. In addition, **4**

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remained intact after prolonged treatment with 3.0 equiv of diborane in THF solution.

To examine the generality of this dephenylation reaction, we applied our best conditions to a series of benzothiazines (Table 1). Compound **6** gave nearly quantitative yield of **7** as a single diastereomer (entry 1). A similar result was obtained for *t*-butyl substrate (entry 2). The reaction worked well for *n*-propyl substrates with essentially complete retention of stereochemistry (entries 3 and 4).

The cyclobutane ring in **14** remained untouched in the presence of strong nucleophilic reducing reagent lithium triethylborohydride. The desired sulfinamide **15** was obtained in 59% yield together with 17% recovered starting material (entry 5). Interestingly, benzothiazine **16** reacted surprisingly fast to afford **17** in excellent yield (reflux, 3 h, entry 6). To our surprise, the labile diene moiety and allyl group stayed intact during the reaction (entries 7, 8). Steric hindrance at C-3 position was tolerated in the dephenylation, and epimerization at C-3 was not observed, as shown in the conversion of **20** to **21** (entry 8). Alcohol **22** was also refluxed with 4.0 equiv of lithium triethylborohydride; the desired sulfinamide **23** was isolated in 70% yield.

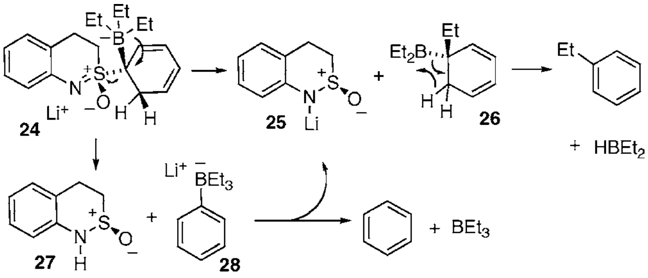
In general, electron rich substituents (Me vs H) on the *S*-aryl ring tended to decrease the reactivity in the dephenylation reaction and result in the longer reaction times. In contrast, an increase of electron density on the *N*-phenyl ring seemed to accelerate the reaction.

To obtain some mechanistic perspective, the crude product from the dephenylation reaction of **4** was subjected to GC−MS. Ethylbenzene was obtained in 44% yield, accompanied by 27% of benzene.

On the basis of our experimental results and precedent,[20] we propose a mechanism for the dephenylation as shown in Scheme 1. The benzothiazine might be converted to **24** via hydride addition. Ethyl group migration and deborylation would afford **25** and **26**, the latter affording ethylbenzene and diethylborane. Alternatively, elimination of sulfinamide from **24** would afford **27** and **28**, which would afford benzene after proton transfer or protic workup.

That dephenylation occurred with retention of configuration at sulfur was unequivically demonstrated by X-ray analyses of **5** and **21**. We thus assume that this trend holds for all substrates examined, as it would be very strange for inversion to occur without apparent cause. The fact that the sulfinamides are produced as single diastereomers also suggests a distinct, single stereochemcal event at the sulfur atom.

Scheme 1. Proposed Dephenylation Mechanism



In summary, we have discovered the first approach toward chiral cyclic sulfinamides from readily available benzothiazines with complete stereocontrol. Preliminary mechanistic studies were carried out and a plausible mechanism was proposed. Further study of this reaction is underway in our laboratory and results will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data and copies of proton and carbon spectra for all new compounds; X-ray data for **5**, **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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