Further Studies of Benzothiazine Metalation

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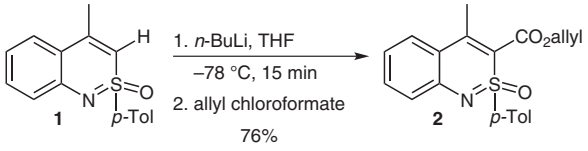
Dedicated to Professor Scott E. Denmark on the occasion of his 60th birthday

Abstract: Treatment of benzothiazines **3** and **8** with butyllithium resulted in deprotonation at C3 to afford the corresponding organolithium species. These compounds could be trapped with a variety of electrophiles to give products in high yield. Some limitations to the processes chiefly based on steric effects were uncovered. Interesting and potentially useful side reactions were also established.

Key words: heterocycles, benzothiazine, metalation, alkylation, sulfoximine

Some years ago, we reported the metalation chemistry of benzothiazine **1** as a means of functionalizing the ring system (Scheme 1).[2] At that time, the methodology we had developed for benzothiazine synthesis produced only racemic species.[3] Later work allowed us to prepare benzothiazines that were essentially enantiomerically pure.[4] This renewed our interest in the functionalization of benzothiazines, as we anticipated that such compounds could be used as chiral ligands[5] or intermediates in natural product synthesis.[6] This report details our study of the scope of metalation of benzothiazines using two substrates as models for the process.



Scheme 1

We began our new studies with what might be called the 'parent' benzothiazine **3**, the simplest structure that could be prepared using our methodology, using the sulfoximine **4** (Figure 1).[7] We quickly found that **3** was as well-behaved as **1** in that lithiation and trapping could be conducted under essentially the same conditions. The results of this work are summarized in Table 1.

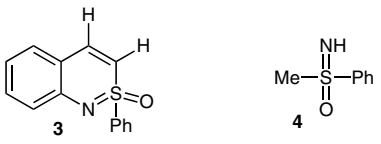


Figure 1

A reasonably diverse selection of electrophiles was studied in order to probe the reactivity of the organolithium species derived from **3**. Several silyl chlorides of various sizes were used to trap the lithiocarbanion. The yields decreased slightly as the steric bulk of the silyl alkyl groups increased, but all yields remained above 80% (Table 1, entries 1–4). Very near stoichiometric amounts of chlorotrimethylsilane were needed to prevent formation of bis-trimethylsilyl product **6** (Figure 2). This type of by-product had been observed in the reaction of the carbanion of **1** with the same electrophile, suggesting polylithiation as a possibility.[2] This phenomenon will be reported elsewhere. Due to what we ascribe to the acidity of our silica gel, loss of the trimethylsilyl group was an issue during chromatography; however, bulkier silyl groups were not removed during chromatography. Interestingly, no products like **6** were observed with other silyl electrophiles.

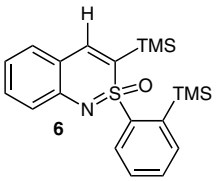


Figure 2

An aromatic aldehyde, 2-bromobenzaldehyde, reacted very smoothly to give the product **5g** in 94% yield as a 1.4:1 mixture of diastereomers (Table 1, entry 7). Both cyclic and acyclic symmetrical ketones were trapped smoothly to give the corresponding products in greater than 85% yields for all examples (Table 1, entries 6, 10, 13, and 17). Ethylene oxide reacted uneventfully to give **5o** in 91% yield (Table 1, entry 15). Polymeric paraformaldehyde provided alcohol **5n** in 76% yield; however, the reaction was very exothermic and could not be reproduced on a larger scale. Other electrophiles such as 1,2-dibromo-1,1,2,2-tetrachloroethane, iodine, and *N*,*N*-dimethylformamide gave very clean reactions in respectable to excellent yields (Table 1, entries 8, 9, and 12).

Two electrophiles failed to provide any products. First, *tert*-butyl bromoacetate neither alkylated in an S_N2 fashion nor reacted at the ester functional group (Table 1, entry 16). The second poor electrophile was diphenylphosphinic chloride (not given in Table 1), which provided no recovered starting material or product. It appeared that many new very polar products were formed, but none could be isolated and identified. Two other elec-

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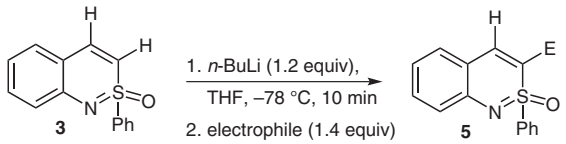
Table 1 Lithiation and Trapping of Benzothiazine **3**



Entry	Electrophile	E	Product	Yield (%)
1	TMSCl	TMS	**5a**	98
2	TESCl	TES	**5b**	94
3	TIPSCl	TIPS	**5c**	94
4	TBSCl	TBS	**5d**	85
5	PhSSPh	SPh	**5e**	38–92
6	benzophenone	$C(OH)Ph_2$	**5f**	91
7	2-Br(C_6H_4)CHO	2-BrC_6H_4(HO)CH	**5g**	94[a]
8	$C_2Br_2Cl_4$	Br	**5h**	81
9	I_2	I	**5i**	96
10	cyclohexanone	$C(OH)(CH_2)_5$	**5j**	97
11	*i*-BuOCOCl	CO_2-*i*-Bu	**5k**	11–51
12	DMF	CHO	**5l**	92
13	pentan-3-one	$C(OH)Et_2$	**5m**	85
14	$(CH_2O)_n$	CH_2OH	**5n**	76
15	oxirane	CH_2CH_2OH	**5o**	91
16	$BrCH_2CO_2Bu$	CH_2CO_2Bu	**5p**	0
17	acetone	$C(OH)Me_2$	**5q**	85

[a] dr = 1.4:1.

trophiles gave particularly large yield ranges; both diphenyl disulfide and isobutyl chloroformate were problematic in achieving respectable yields consistently. During the isolation of sulfide **5e**, the most polar components were flushed off the silica gel column and collected in a vial; a single crystal grew out of this residue. An X-ray quality crystal was obtained and evidence for new benzothiazine reactivity was seen. Perhaps not surprisingly, the carbanion derived from **3** was apparently able to add to the product **5e** to afford **7** (Figure 3).[8]

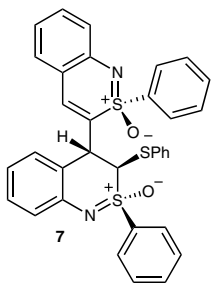


Figure 3

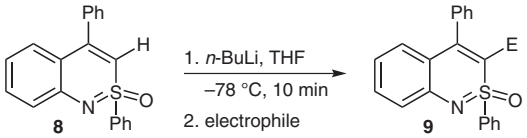
We next turned our attention to the 4-phenyl-substituted benzothiazine **8**. This was easily accessible using methodology that we had already developed and afforded a steric impediment at the lithiation site, a feature we desired to explore in more detail.

The scope of our studies with **8** were not as broad as those with **3**, as certain electrophiles proved too bulky to react. Nevertheless, they were clearly indicative of a steric effect in the efficacy of the reaction of the carbanion derived from **8** with electrophiles. Furthermore, certain electrophiles that proved untenable with **3** could be used with **8**. The results are shown in Table 2.

The reactivity pattern of **8** was quite different from that of **3**. Chlorotriisopropylsilane did not react with the sulfoximine-stabilized vinyl carbanion of benzothiazine **8**, most likely due to steric effects (Table 2, entry 1). Both the enolizable acetone and non-enolizable benzophenone were unreactive with the organolithium derived from **8**, although they were very reactive with **3** (Table 2, entries 2 and 3). Note that benzaldehyde reacted smoothly to give **9f** in 75% yield with slightly improved diastereoselectivity as compared to **3**. This increase in diastereomeric ratio is likely due to steric crowding near the adjacent 4-phenyl substituent.

It is most likely the case that benzothiazine **8** is sufficiently hindered that conjugate addition becomes slow. Indeed, the conjugate base of **8** reacted with disulfides in high yield, except for the very sterically hindered di-*tert*-butyl disulfide, which led to only an approximately 19% yield

Table 2 Lithiation and Trapping of Benzothiazine **8**



Entry	Electrophile	E	Product	Yield (%)
1	TIPSCl	TIPS	**9a**	0
2	acetone	$C(OH)Me_2$	**9b**	0
3	benzophenone	$C(OH)Ph_2$	**9c**	0
4	I_2	I	**9d**	74
5	$C_2Br_2Cl_4$	Br	**9e**	95
6	PhCHO	CH(OH)Ph	**9f**	75[a]
7	MeSSMe	SMe	**9g**	98
8	PhSSPh	SPh	**9h**	94
9	EtSSEt	SEt	**9i**	88
10	CySSCy	SCy	**9j**	98
11	*t*-BuSS*t*-Bu	S*t*-Bu	**9k**	19

[a] dr = 2.4:1.

of product (Table 2, entry 11); this compound was not completely characterized.

We obtained evidence that electrophiles of the type R_2PCl reacted with both anions used in this work. However, problems with phosphorus oxidation have, as yet, precluded the isolation of products of suitable quality for rigorous characterization. Further studies are necessary to resolve this difficulty.

In conclusion, we have demonstrated some of the scope of the lithiation and electrophilic trapping of two 2,1-benzothiazines. Since these species can be made in enantiomerically pure form, it is conceivable that certain modifications could lead to families of chiral ligands that are useful in asymmetric catalysis. Further results will be reported in due course.

All reactions performed were carried out under anhydrous conditions involving either N_2 or argon gas. Glassware was oven dried (125 °C) and cooled by a continuous flow of dry N_2. Solvents were distilled under anhydrous and O_2-free conditions. Et_2O, toluene, and THF were dried over Na metal and O_2 was removed by generation of a benzophenone ketyl. CH_2Cl_2 was dried over CaH_2 in a dry N_2 atmosphere. In most cases, reagents were distilled prior to use if liquid; solids reagents were crystallized or used directly from a newly purchased commercial container. Handling of pyrophoric reagents, namely organometallic reagents, was performed with glass, gastight syringes, rubber septa, and argon-filled balloons. Air and moisture sensitive reagents were handled with a dry N_2-filled plastic glove bag. Molecular sieves were freshly activated by heating to 200 °C under full vacuum (<2.67 mbar) for several hours. Reaction mixtures were concentrated using rotary evaporators with both water aspiration and pneumatic vacuum pump sources depending on the boiling point of the solvent removed; residual solvent was removed by full vacuum when necessary. Silica gel used in chromatographic separations was purchased from Silicycle (230–400 mesh). Reactions were monitored by glass-backed silica gel TLC plates purchased from Sigma Aldrich and visualized using UV irradiation. Melting points were obtained on a Fisher-Johns melting point apparatus. IR spectra were recorded via a liquid NaCl chamber on a Perkin Elmer 1600 series FT-IR spectrophotometer. ^1H and ^{13}C NMR were taken on one of three Bruker ARX-250, ARX-300, or ARX-500 Ultrashield spectrometers with internal TMS standard ($\delta = 0.0$); spectra were taken as $CDCl_3$ solns. ^{13}C NMR spectra taken were ^1H decoupled and contained a $CDCl_3$ ($\delta = 77.0$) internal standard. HRMS were analyzed by a Bruker 12 Tesla Apex-Qe FTICR-MS with an Apollo II ion source.

2-Phenyl-3-(trimethylsilyl)-2,1-benzothiazine 2-Oxide (5a); Typical Procedure A for Lithiation

To an oven-dried, N_2-cooled flask with stirbar, benzothiazine **3** (0.107 g, 0.443 mmol) was added and covered with a rubber septum. The flask was charged with argon, and freshly distilled THF (4 mL) was added via syringe. The reaction was then cooled to –78 °C with a dry ice/acetone bath. Then 2.08 M BuLi (0.256 mL, 0.532 mmol) was added dropwise to the cooled soln resulting in a dark orange soln. After 10 min, TMSCl (0.0793 mL, 0.621 mmol) was added through the rubber septum by syringe. The mixture was stirred further for up to 3 h (or until completion was observed by TLC). The mixture was quenched with sat. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL); the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography [silica gel, 25% EtOAc–hexane; TLC $R_f = 0.40$ (25% EtOAc–hexanes), yellow long UV spot] afforded **5a** (0.136 g, 98%) as a yellow solid.

3-Iodo-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9d); Typical Procedure B for Lithiation

To an oven-dried, N_2-cooled flask with stirbar, benzothiazine **8** (0.052 g, 0.164 mmol) was added and covered with a rubber septum. The flask was charged with argon, and freshly distilled THF (2 mL) was added via syringe. The reaction was then cooled to –78 °C with a dry ice/acetone bath. Then 2.10 M BuLi (0.0936 mL, 0.196 mmol) was added dropwise to the cooled soln resulting in a dark orange soln. After 10 min, I_2 (0.0582 g, 0.229 mmol) was added in THF (1 mL) through the rubber septum by syringe. The mixture was stirred further for up to 3 h (or until completion was observed by TLC). The mixture was quenched with sat. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL); the combined organic extracts were dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography [silica gel, 25% EtOAc–hexane; TLC $R_f = 0.24$ (25% EtOAc–hexanes). green long UV spot] afforded **9d** (0.537 g, 74%) as an orange solid.

2-Phenyl-3-(trimethylsilyl)-2,1-benzothiazine 2-Oxide (5a)

Typical procedure A; yellow solid; yield: 136 mg (98%); mp 183 °C.

IR (NaCl): 3015, 2964, 1605, 1577, 1531, 1308, 1289, 1254, 1206, 990, 845, 729, 426 cm^{-1}.

^1H NMR: (250 MHz, $CDCl_3$): δ = 0.05 (s, 9 H), 6.99 (t, J = 8.0 Hz, 1 H), 7.24 (d, J = 7.9 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 7.43 (t, J = 6.9 Hz, 1 H), 7.49–7.63 (m, 3 H), 7.74 (s, 1 H), 7.87 (d, J = 7.0 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –0.7, 116.3, 119.7, 121.4, 123.7, 128.7, 129.3, 129.7, 132.3, 133.2, 142.5, 145.6, 146.0.

HRMS: m/z $[M + Na]^+$ calcd for $C_{17}H_{19}NOSSiNa$: 336.0849; found: 336.0851.

2-Phenyl-3-(triethylsilyl)-2,1-benzothiazine 2-Oxide (5b)

Typical procedure A; yellow solid; yield: 143 mg (94%); mp 60 °C.

IR (NaCl): 2959, 2912, 2878, 1605, 1576, 1529, 1308, 1289, 1308, 1224, 1127, 1004, 848, 787, 723, 667, 580, 438 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.30–0.44 (m, 3 H), 0.63–0.71 (m, 3 H), 0.84 (t, J = 7.7 Hz, 9 H), 6.98 (t, J = 6.8 Hz, 1 H), 7.24 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 7.42 (t, J = 8.4 Hz, 1 H), 7.47–7.62 (m, 3 H), 7.71 (s, 1 H), 7.87 (d, J = 6.9 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 3.1, 6.8, 116.1, 118.4, 119.5, 123.5, 128.4, 129.0, 129.6, 132.1, 133.1, 142.7, 145.5, 147.0.

HRMS: m/z $[M + Na]^+$ calcd for $C_{20}H_{25}NOSSiNa$: 378.1318; found: 378.1313.

2-Phenyl-3-(triisopropylsilyl)-2,1-benzothiazine 2-Oxide (5c)

Typical procedure A; orange solid; yield: 64 mg (94%); mp 115 °C.

IR (NaCl): 3013, 2949, 2869, 1605, 1527, 1467, 1448, 1313, 1206, 1127, 1097, 988, 883, 844, 787, 727, 684, 643, 478 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.75 (d, J = 6.6 Hz, 9 H), 0.95–1.11 (m, 12 H), 6.88 (t, J = 7.5 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 7.25 (d, J = 7.7 Hz, 1 H), 7.32 (t, J = 8.5 Hz, 1 H), 7.34–7.50 (m, 3 H), 7.69 (s, 1 H), 7.75 (d, J = 6.7 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 11.7, 18.2, 18.5, 115.8, 117.2, 119.4, 123.3, 128.4, 128.8, 129.7, 132.3, 133.0, 144.1, 145.4, 148.7.

HRMS: m/z $[M + Na]^+$ calcd for $C_{23}H_{31}NOSSiNa$: 420.1788; found: 420.1791.

3-(*tert*-Butyldimethylsilyl)-2-phenyl-2,1-benzothiazine 2-Oxide (5d)

Typical procedure A; yellow solid; yield: 58 mg (85%); mp 117 °C.

IR (NaCl): 3067, 3015, 1605, 1579, 1531, 1286, 1224, 1206, 1097, 991, 728, 685, 438 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = -0.20 (s, 3 H), 0.17 (s, 3 H), 0.87 (s, 9 H), 6.97 (t, J = 8.1 Hz, 1 H), 7.21 (d, J = 8.3 Hz, 1 H), 7.34 (d,

J = 7.8 Hz, 1 H), 7.41 (t, J = 8.3 Hz, 1 H), 7.48–7.60 (m, 3 H), 7.80–7.84 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1, –4.8, 17.7, 26.5, 115.8, 119.0, 119.6, 123.5, 128.5, 128.9, 129.7, 132.4, 132.9, 143.7, 145.4, 148.3.

HRMS: m/z [M + Na]$^+$ calcd for $C_{20}H_{25}NOSSiNa$: 378.1318; found: 378.1315.

2-Phenyl-3-(phenylthio)-2,1-benzothiazine 2-Oxide (5e)
Typical procedure A; yellow solid; yield: 177 mg (38–92%); mp 104 °C.

IR (NaCl): 3015, 2960, 2860, 1605, 1575, 1529, 1468, 1310, 1257, 1205, 1097, 988, 844, 811, 728, 667 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.05 (t, J = 8.0 Hz, 1 H), 7.11 (s, 5 H), 7.32–7.54 (m, 7 H), 7.80 (d, J = 7.2 Hz, 1 H), 7.98 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 116.0, 118.5, 120.4, 124.0, 127.2, 128.5, 128.9, 129.2, 129.7, 130.1, 132.8, 133.4, 134.6, 138.5, 145.4, 147.9.

HRMS: m/z [M + Na]$^+$ calcd for $C_{20}H_{15}NOS_2Na$: 372.0487; found: 372.0470.

3-(Hydroxydiphenylmethyl)-2-phenyl-2,1-benzothiazine 2-Oxide (5f)
Typical procedure A; tan solid; yield: 80 mg (91%); mp 176 °C.

IR (NaCl): 3579, 3064, 3018, 1608, 1447, 1292, 1223, 1206, 1188, 729, 702, 471, 445 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.86 (br s, 1 H), 6.97–7.10 (m, 6 H), 7.15–7.47 (m, 12 H), 7.59 (d, J = 7.2 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 81.6, 116.6, 120.3, 123.5, 126.6, 127.1, 127.6, 127.9, 128.0, 128.3, 128.4, 130.0, 130.3, 131.9, 132.6, 138.3, 139.5, 141.3, 144.4, 145.8.

HRMS: m/z [M + Na]$^+$ calcd for $C_{27}H_{21}NO_2SNa$: 446.1185; found: 446.1185.

3-[(2-Bromophenyl)(hydroxy)methyl]-2-phenyl-2,1-benzothiazine 2-Oxide (5g)
Typical procedure A; off-white solid; yield: 104 mg (94% overall); racemic mixture of 2 diastereomers (1.4:1).

Major Diastereomer
Mp 204 °C.

IR (NaCl): 3540, 3068, 3015, 1612, 1446, 1288, 1217, 1185, 1129, 1096, 1014, 991, 831, 771, 534 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (d, J = 2.3 Hz, 1 H), 5.57 (d, J = 1.6 Hz, 1 H), 6.94 (s, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 7.15–7.21 (m, 2 H), 7.32 (d, J = 8.1 Hz, 1 H), 7.39–7.46 (m, 3 H), 7.53–7.58 (m, 2 H), 7.65 (t, J = 7.3 Hz, 1 H), 7.78 (d, J = 7.7 Hz, 1 H), 8.00 (d, J = 7.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.4, 116.8, 120.5, 122.2, 123.4, 123.6, 127.7, 128.9, 129.0, 129.7, 130.1, 130.3, 132.2, 132.7, 133.7, 137.0, 137.5, 138.0, 144.7.

HRMS: m/z [M + Na]$^+$ calcd for $C_{21}H_{16}BrNO_2SNa$: 447.9977; found: 447.9979.

Minor Diastereomer
Mp 193 °C.

IR (NaCl): 3592, 3067, 3014, 1612, 1545, 1446, 1343, 1292, 1227, 1194, 1097, 991, 775, 765, 521 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (d, J = 5.7 Hz, 1 H), 5.90 (d, J = 5.6 Hz, 1 H), 7.03 (t, J = 8.1 Hz, 1 H), 7.08 (t, J = 7.7 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.33 (m, 7 H), 7.65 (s, 1 H), 7.70 (d, J = 7.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.3, 116.7, 120.3, 121.8, 122.6, 123.4, 127.6, 128.7, 129.1, 129.1, 129.9, 130.0, 132.2, 132.9, 133.2, 138.6, 139.3, 140.5, 144.7.

HRMS: m/z [M + Na]$^+$ calcd for $C_{21}H_{16}BrNO_2SNa$: 447.9977; found: 448.0019.

3-Bromo-2-phenyl-2,1-benzothiazine 2-Oxide (5h)
Typical procedure A; yellow solid; yield: 12 mg (81%); mp 105 °C.

IR (NaCl): 3069, 3014, 2930, 1604, 1535, 1444, 1342, 1288, 1225, 1206, 1098, 995, 918, 786, 728, 569, 534 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (t, J = 7.4 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.56–7.70 (m, 3 H), 7.82 (s, 1 H), 7.93 (d, J = 7.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 103.2, 118.6, 120.8, 123.8, 128.8, 128.9, 130.1, 132.1, 133.9, 138.4, 141.3, 143.5.

HRMS: m/z [M + Na]$^+$ calcd for $C_{14}H_{10}BrNOSNa$: 341.9559; found: 341.9570.

3-Iodo-2-phenyl-2,1-benzothiazine 2-Oxide (5i)
Typical procedure A; orange solid; yield: 76 mg (96%); mp 103 °C.

IR (NaCl): 3069, 3014, 1604, 1528, 1342, 1288, 1207, 1097, 992, 787, 729, 434, 426 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.04 (t, J = 7.3 Hz, 1 H), 7.26–7.35 (m, 2 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.55–7.70 (m, 3 H), 7.91 (d, J = 6.9 Hz, 2 H), 8.03 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 74.2, 118.9, 120.5, 123.9, 128.7, 128.8, 130.0, 132.3, 133.8, 139.5, 144.2, 148.6.

HRMS: m/z [M + Na]$^+$ calcd for $C_{14}H_{10}INOSNa$: 389.9420; found: 389.9421.

3-(1-Hydroxycyclohexyl)-2-phenyl-2,1-benzothiazine 2-Oxide (5j)
Typical procedure A; yellow-tan solid; yield: 47 mg (97%); mp 135 °C.

IR (NaCl): 3574, 3016, 2939, 2861, 1608, 1447, 1343, 1295, 1224, 1206, 1096, 993, 787, 728, 523, 467, 430 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08–1.22 (m, 1 H), 1.38–1.92 (m, 9 H), 2.07 (s, 1 H), 7.01 (t, J = 8.0 Hz, 1 H), 7.23 (d, J = 7.9 Hz, 1 H), 7.33 (d, J = 7.8 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 1 H), 7.48–7.60 (m, 3 H), 7.61 (s, 1 H), 7.83 (d, J = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 21.5, 25.0, 38.3, 40.5, 74.0, 116.4, 120.0, 123.1, 128.5, 128.9, 129.4, 130.1, 131.6, 132.8, 135.6, 143.8, 143.9.

HRMS: m/z [M + Na]$^+$ calcd for $C_{20}H_{21}NO_2SNa$: 362.1185; found: 362.1178.

Isobutyl 2-Phenyl-2,1-benzothiazine-3-carboxylate 2-Oxide (5k)
Typical procedure A; yellow solid; yield: 8–21 mg (11–51%); mp 93 °C.

IR (NaCl): 3027, 2963, 2875, 1712, 1609, 1533, 1448, 1287, 1206, 1152, 1098, 986, 469 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.74 (d, J = 6.7 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H), 1.75 (septet, J = 6.7 Hz, 1 H), 1.38–1.92 (dd, J_1 = 6.7 Hz, J_2 = 3.8 Hz, 2 H), 7.07 (t, J = 7.1 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 7.49–7.65 (m, 5 H), 7.92 (d, J = 6.7 Hz, 2 H), 8.56 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.9, 18.9, 27.5, 72.0, 111.8, 116.3, 120.7, 124.0, 128.5, 129.3, 131.3, 133.2, 134.8, 141.5, 145.7, 147.3, 161.9.

HRMS: m/z [M + Na]$^+$ calcd for $C_{19}H_{19}NO_3SNa$: 364.0978; found: 364.0968.

2-Phenyl-2,1-benzothiazine-3-carbaldehyde 2-Oxide (5l)
Typical procedure A; yellow solid; yield: 45 mg (92%); mp 119 °C.

IR (NaCl): 3022, 2928, 2855, 1688, 1609, 1586, 1531, 1291, 1223, 1206, 1153, 729, 426 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 7.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.50–7.68 (m, 5 H), 7.96 (d, *J* = 7.2 Hz, 2 H), 8.23 (s, 1 H), 9.57 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 116.4, 119.1, 121.2, 124.6, 128.8, 129.9, 131.5, 133.8, 135.9, 139.5, 147.2, 148.6, 184.7.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{11}NO_2SNa$: 292.0403; found: 292.0345.

3-(3-Hydroxypentan-3-yl)-2-phenyl-2,1-benzothiazine 2-Oxide (5m)
Typical procedure A; tan solid; yield: 12 mg (85%); mp 156 °C.

IR (NaCl): 3574, 3018, 2975, 1608, 1446, 1344, 1296, 1224, 1206, 1094, 989, 792, 668, 528 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.63 (t, *J* = 7.4 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 1.38 (sextet, *J* = 6.9 Hz, 1 H), 1.64 (sextet, *J* = 7.3 Hz, 1 H), 1.77 (q, *J* = 7.4 Hz, 2 H), 2.50 (s, 1 H), 7.02 (t, *J* = 7.0 Hz, 1 H), 7.27 (d, *J* = 7.3 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 1 H), 7.37 (s, 1 H), 7.42 (t, *J* = 8.4 Hz, 1 H), 7.48–7.60 (m, 3 H), 7.85 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.5, 7.9, 33.3, 34.9, 78.2, 116.4, 120.1, 123.2, 126.5, 128.4, 129.5, 131.6, 133.0, 136.2 143.0, 144.1.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{21}NO_2SNa$: 350.1185; found: 350.1179.

3-(Hydroxymethyl)-2-phenyl-2,1-benzothiazine 2-Oxide (5n)
Typical procedure A; orange solid; yield: 47 mg (76%); mp 134 °C.

IR (NaCl): 3601, 3465, 3067, 3014, 2874, 1616, 1447, 1340, 1287, 1224, 1205, 1097, 991, 728, 686, 666, 532 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (br s, 1 H), 4.36 (s, 2 H), 7.05 (t, *J* = 8.1 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.46 (t, *J* = 6.9 Hz, 1 H), 7.54–7.70 (m, 4 H), 7.90 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.7, 116.9, 120.5, 121.6, 123.7, 129.1, 129.4, 129.7, 132.0, 133.6, 137.4, 139.3, 144.7.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{13}NO_2SNa$: 294.0559; found: 294.0573.

3-(2-Hydroxyethyl)-2-phenyl-2,1-benzothiazine 2-Oxide (5o)
Typical procedure A; yellow solid; yield: 29 mg (91%); mp 74 °C.

IR (NaCl): 3620, 3487, 3067, 3016, 1613, 1447, 1289, 1223, 1206, 1099, 993, 729, 470, 426 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.37–2.46 (m, 1 H), 2.58–2.67 (m, 1 H), 3.66–3.85 (m, 2 H), 7.02 (t, *J* = 7.1 Hz, 1 H), 7.27–7.35 (m, 2 H), 7.42 (t, *J* = 8.1 Hz, 1 H), 7.48 (s, 1 H), 7.51–7.67 (m, 4 H), 7.89 (d, *J* = 6.7 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.1, 62.0, 117.3, 120.1, 120.4, 123.5, 129.1, 129.1, 129.5, 131.4, 133.5, 138.1, 138.9, 143.8.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{15}NO_2SNa$: 308.0716; found: 308.0726.

3-(2-Hydroxypropan-2-yl)-2-phenyl-2,1-benzothiazine 2-Oxide (5q)
Typical procedure A; green-tan solid; yield: 473 mg (85%); mp 175 °C.

IR (NaCl): 3534, 2975, 2361, 1608, 1546, 1447, 1345, 1322, 1296, 1202, 990, 910, 521, 507, 502, 408 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.50 (s, 3 H), 2.58 (br s, 1 H), 7.00 (t, *J* = 7.5 Hz, 1 H), 7.24 (d, *J* = 7.9 Hz, 1 H), 7.36 (d, *J* = 5.9 Hz, 1 H), 7.41 (t, *J* = 8.5 Hz, 1 H), 7.46–7.61 (m, 3 H), 7.63 (s, 1 H), 7.85 (d, *J* = 6.7 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 30.9, 32.6, 72.6, 116.5, 120.1, 123.0, 128.6, 129.3, 129.4, 129.5, 131.6, 133.0, 135.4, 142.8, 143.8.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{17}NO_2SNa$: 322.0872; found: 322.0869.

3-Iodo-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9d)
Typical procedure B; orange solid; yield: 38 mg (74%); mp 83 °C.

IR (NaCl): 3064, 2928, 2855, 2252, 1600, 1566, 1515, 1490, 1326, 1249, 1218, 1098, 996, 959, 699, 650, 589, 545, 508, 499, 473 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.84 (t, *J* = 8.2 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 7.07–7.11 (m, 1 H), 7.24–7.68 (m, 9 H), 7.99 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 80.9, 119.2, 120.3, 124.0, 128.0, 128.6, 128.7, 129.0, 130.1, 131.9, 133.7, 140.1, 140.9, 144.6, 156.3.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{14}INOSNa$: 465.9733; found: 465.9728.

3-Bromo-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9e)
Typical procedure B; yellow solid; yield: 76 mg (95%); mp 174 °C.

IR (NaCl): 3065, 2927, 2855, 1600, 1567, 1523, 1492, 1330, 1252, 1222, 1098, 970, 605, 589, 545, 495, 476, 447, 408 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.88–7.01 (m, 2 H), 7.16–7.18 (m, 1 H), 7.39–7.71 (m, 9 H), 8.05 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 104.1, 119.7, 120.5, 124.1, 128.4, 128.5, 128.7, 128.9, 130.1, 131.6, 131.9, 133.8, 136.9, 138.7, 143.8, 150.8.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{14}BrNOSNa$: 417.9872; found: 417.9866.

3-[Hydroxy(phenyl)methyl]-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9f)
Typical procedure B; tan solid; yield: 80 mg (75%); inseparable 2.4:1 diastereomeric mixture characterized as a mixture.

IR (NaCl): 3468, 3064, 2924, 2854, 1601, 1572, 1530, 1336, 1248, 1248, 1208, 1190, 1153, 1127, 1039, 541, 538 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ (major diastereomer) = 3.60 (d, *J* = 5.2 Hz, 1 H), 5.78 (d, *J* = 5.2 Hz, 1 H), 7.64 (d, *J* = 7.4 Hz, 2 H); δ (minor diastereomer) = 2.59 (s, 0.4 H), 5.60 (s, 0.4 H), 7.96 (d, *J* = 6.7 Hz, 0.8 H); remaining: 6.68–7.42 (m, 25 H; 18 × 1 for major + 0.4 × 18 for minor = 25).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 70.6, 70.9, 118.7, 102.1, 124.1, 124.8, 125.4, 126.3, 127.5, 127.6, 127.8, 128.1, 128.3, 128.5, 128.6, 128.8, 129.2, 129.6, 130.4, 131.5, 132.9, 135.5, 139.8, 140.7, 144.6, 148.6.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{21}NO_2SNa$: 446.1185; found: 446.1183.

3-(Methylthio)-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9g)
Typical procedure B; yellow solid; yield: 74 mg (98%); mp 137 °C.

IR (NaCl): 3065, 3045, 2925, 1601, 1562, 1515, 1490, 1448, 1332, 1245, 1210, 1153, 1097, 996, 971, 821, 590, 550, 491, 463, 431, 428 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 3 H), 6.81–6.86 (m, 1 H), 6.91 (d, *J* = 7.8 Hz, 1 H), 7.12–7.15 (m, 1 H), 7.37–7.63 (m, 9 H), 8.03 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 116.0, 119.1, 119.7, 124.1, 128.1, 128.1, 128.2, 128.2, 128.4, 128.8, 129.0, 129.8, 131.9, 133.2, 136.3, 139.5, 145.1, 157.4.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{17}NOS_2Na$: 386.0644; found: 386.0640.

2,4-Diphenyl-3-(phenylthio)-2,1-benzothiazine 2-Oxide (9h)
Typical procedure B; yellow solid; yield: 255 mg (94%); mp 120 °C.

IR (NaCl): 3065, 3042, 2926, 1601, 1560, 1512, 1490, 1331, 1244, 1213, 1153, 1097, 995, 972, 819, 684, 590, 553, 474, 444, 441 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81–6.89 (m, 3 H), 6.95–6.98 (m, 4 H), 7.07–7.11 (m, 1 H), 7.21–7.48 (m, 9 H), 7.93 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.7, 119.6, 119.9, 124.3, 126.3, 127.9, 128.2, 128.3, 128.3, 128.4, 128.7, 128.8, 129.3, 129.7, 130.3, 132.3, 133.2, 135.2, 135.8, 138.3, 145.7, 158.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{19}NOS_2Na$: 448.0800; found: 448.0797.

3-(Ethylthio)-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9i)
Typical procedure B; yellow solid; yield: 213 mg (88%); mp 164 °C.

IR (NaCl): 3066, 3048, 2929, 1601, 1561, 1514, 1490, 1448, 1331, 1245, 1210, 1154, 1097, 996, 971, 821, 685, 590, 550, 467, 403 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.4 Hz, 3 H), 2.33–2.43 (m, 2 H), 6.81–6.87 (m, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 7.10–7.13 (m, 1 H), 7.35–7.44 (m, 5 H), 7.45–7.64 (m, 4 H), 8.02 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 32.2, 115.0, 119.2, 119.7, 124.1, 128.0, 128.1, 128.1, 128.4, 128.6, 129.0, 129.1, 129.9, 131.8, 133.2, 136.4, 139.5, 145.1, 157.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{19}NOS_2Na$: 400.0800; found: 400.0797.

3-(Cyclohexylthio)-2,4-diphenyl-2,1-benzothiazine 2-Oxide (9j)
Typical procedure B; yellow solid; yield: 270 mg (98%); mp 56 °C.

IR (NaCl): 3023, 2932, 2854, 1600, 1560, 1512, 1490, 1449, 1331, 1245, 1213, 1153, 1096, 970, 820, 618, 590, 479, 473, 403 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71–0.82 (m, 1 H), 0.91–0.98 (m, 4 H), 1.39–1.58 (m, 5 H), 2.45–2.52 (m, 1 H), 6.79–6.88 (m, 1 H), 6.95 (d, *J* = 8.2 Hz, 1 H), 7.09–7.14 (m, 1 H), 7.36–7.45 (m, 5 H), 7.47–7.64 (m, 4 H), 8.03 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 25.6, 25.7, 32.5, 32.8, 49.8, 115.1, 119.2, 119.7, 124.1, 127.9, 128.0, 128.4, 128.9, 129.0, 129.6, 130.1, 133.1, 136.3, 139.5, 145.1, 156.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}NOS_2Na$: 454.1270; found: 454.1270.

3-(*tert*-Butylthio)-2,4-diphenylbenzo[*c*][1,2]thiazine 2-Oxide (9k)
Typical procedure B; orange semi-solid; yield: 50 mg (19%).

IR (NaCl): 3463, 3061, 2925, 1601, 1571, 1529, 1448, 1321, 1247, 1193, 1154, 1097, 991, 699, 682, 603, 523, 504, 499, 439 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (s, 9 H), 6.86 (t, *J* = 8.2 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 7.13–7.62 (m, 20 H), 7.97 (d, *J* = 6.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.4, 50.1, 119.3, 119.7, 124.3, 127.6, 127.9, 128.2, 128.4, 129.6, 129.9, 130.4, 130.6, 132.1, 133.1, 136.8, 140.1, 145.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{23}NOS_2Na$: 428.1113; found: 428.1115.

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(8) Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 930341 (**5f**), 930342 (**5g**), 930343 (**5j**), 930344 (**5m**), 930345 (**5n**), 930346 (**5q**), and 930340 (**7**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

