Tetrahedron 66 (2010) 3228–3241

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot synthesis of unsymmetrical disulfides using 1-chlorobenzotriazole as oxidant: Interception of the sulfenyl chloride intermediate

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ARTICLE INFO

Article history:
Received 15 October 2009
Received in revised form
5 February 2010
Accepted 22 February 2010
Available online 25 February 2010

Keywords:
1-Chlorobenzotriazole
Unsymmetrical disulfide
Cystine

ABSTRACT

A high-yielding and low temperature one-pot procedure is described for unsymmetrical disulfide synthesis from two different thiols using 1-chlorobenzotriazole (BtCl) as oxidant. The mechanism of the coupling involves in situ trapping of the sulfenyl chloride intermediate R^1SCl by nucleophilic benzotriazole (BtH) to form R^1SBt, which protects R^1SCl from forming the homodimer R^1SSR^1. The methodology is applicable to all types of thiol (aliphatic, aromatic, heteroaromatic), with a variation developed for aliphatic–aliphatic couplings. Differentially N-protected cysteines couple to afford the unsymmetrical cystine derivatives in high yield (90%), which serves as a model for the one-pot intermolecular coupling of cysteine-containing peptides to form peptide disulfide heterodimers. Minimal exchange in aromatic–aromatic disulfide synthesis is noted on account of the mild conditions.

1. Introduction

Whilst many oxidants exist for the efficient conversion of a thiol into its symmetrical disulfide, the synthesis of an unsymmetrical disulfide in an efficient manner from two different thiols is a far more subtle methodological challenge in view of the possibility of forming three possible disulfide products as R^1SSR^1 (homodimer 1), R^2SSR^2 (homodimer 2) and the desired R^1SSR^2 (heterodimer). Published methods for this transformation are based mainly on the coupling of two different thiols via activating one of them to a sulfenyl derivative. Alternatively, though less conveniently, one may access the sulfenyl derivative by cleavage of a symmetrical disulfide with an electrophilic reagent, in which case the disulfide must be available. By comparison, methodologies for unsymmetrical disulfide synthesis from a symmetrical disulfide or via miscellaneous groups without the intervention of a sulfenyl derivative are far less common,[1] with a recently reported rhodium-catalysed disulfide exchange protocol holding the most promise.[2] The sulfenyl-based methodology involving thiols as starting materials involves using an electrophilic reagent to convert one of them into a sulfenyl derivative R^1SLG (LG=Leaving Group), which can then be used as a sulfur electrophile in a nucleophilic substitution (thiolysis) reaction with a second thiol to form the desired product. In this regard, a plethora of different leaving groups based on different heteroatoms have been identified with varying levels of reactivity. Scheme 1 reveals the various equations involved in the methodology, and highlights a major potential drawback in that R^1SLG, once formed, can go on to react with thiol 1 to form homodimer 1 resulting in the formation of a high percentage of homodimer 1 (Eq. 2) depending on the ratio of k_1/k_2.

$$R^1SH \xrightarrow[k_1]{\text{Electrophilic reagent}} R^1SLG \qquad \text{eqn 1}$$

$$R^1SLG + R^1SH \xrightarrow{k_2} R^1SSR^1 \qquad \text{eqn 2}$$

$$R^1SLG + R^2SH \xrightarrow{k_3} R^1SSR^2 \qquad \text{eqn 3}$$

Scheme 1. Sulfenyl methodology for unsymmetrical disulfide formation from two different thiols.

If R^1SLG is a reactive intermediate that is difficult to isolate, inevitably it gets transformed as a mixture, Scheme 1. Indeed, the first reported example a hundred years ago by Zincke[3] of R^1SLG formation from a thiol in the form of a sulfenyl chloride illustrates this point in that reaction of thiophenol with chlorine resulted in the formation of both diphenyl disulfide (homodimer 1) and benzenesulfenyl chloride. Over the years, the range of leaving groups have diversified but the aforementioned principle has remained. Thus, following pioneering work by Swan on Bunte salts (thiosulfates),[4] Hiskey on sulfenylthiocyanates,[5] Mukaiyama on sulfenylhydrazides using DEAD[6] and Harpp and Boustang simultaneously on sulfenylimides[7] over a period spanning the 1950s through to the 1970s, other *S*-based groups[8–12] to include bis-heteroaromatic disulfides[13–15] as an extremely popular variant as well as other N-based[16,17] leaving groups have followed to the present day.

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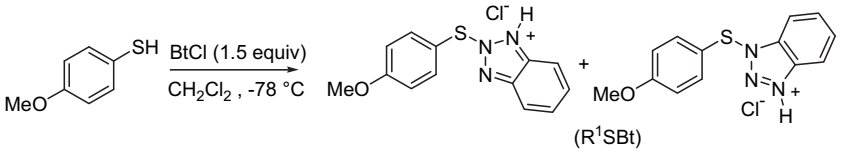
doi:10.1016/j.tet.2010.02.077

As a result of thiol competition in Eq. 2 of Scheme 1, the aforementioned sulfenyl methodologies have inevitably involved at least a two-step procedure with a purification step for R^1SLG where possible. A major drawback of most of these methods, however, is the need to use a harsh, toxic electrophilic agent such as bromine, thionyl chloride or sulfuryl chloride to gain access to R^1SLG. For instance, sulfenimides as one of the more popular types still in modern usage are prepared most conveniently from a disulfide, an imide such as phthalimide and bromine.[18] The exceptions are the isomeric Bt derivatives of the thiol assigned overall as R^1SBt. The appearance of colour in the reaction initially, which faded over time, is consistent with the formation of the arylsulfenyl chloride, and thus it was concluded that formation of R^1SBt proceeds via formation of R^1SCl followed by rapid interception by the nucleophilic BtH (Scheme 2). R^1SBt reacts a lot slower with incoming thiol at this temperature compared to the rate of reaction of thiol with BtCl as evidenced (TLC) by the lack of formation of dianisyl disulfide homodimer 1.



Scheme 2. In situ trapping of R^1SH to R^1SBt.

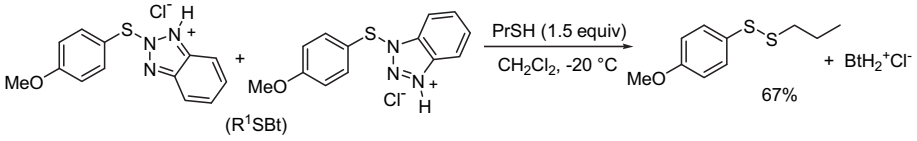
cluster of reactions involving heteroaromatic disulfides such as bis-benzothiazoyl disulfide,[14] in which R^1SLG can be relatively easily accessed as a stable intermediate via exchange of R^1SH with the disulfide. However, here too, some degree of homodimer 1 production is inevitable from over-reaction with R^1SH.

In response to this overall limitation, we have recently introduced a new methodology[19] involving 1-chlorobenzotriazole as the oxidant in a one-pot transformation that minimizes the formation of homodimer 1. 1-Chlorobenzotriazole (BtCl) was introduced as a novel oxidant in 1968 by Rees[20] and may be cheaply and readily prepared in multigram quantities by the oxidation of benzotriazole (BtH) with bleach in aqueous acetic acid. The product precipitates out of solution and can be crystallized and stored in the refrigerator for long periods. Although BtCl has found usage as both an oxidant as well as a chlorinating agent in synthetic organic chemistry, its application to sulfur chemistry has not developed. Our new methodology for one-pot unsymmetrical disulfide synthesis using BtCl owes its innovation to an in situ trapping step, in which the initial formed R^1SCl (as R^1SLG) is 'protected' from further thiol attack by rapid transformation into R^1SBt (trapped R^1SLG), which undergoes minimal reaction with R^1SH under the conditions of its formation (−78 °C), because $k_2 << k_1$ (Scheme 1) where k_2 refers to trapped R^1SLG. Subsequent reaction with R^2SH may then proceed with overall minimization of homodimer 1 formation. In this full paper, we give a full account of the development and scope of our novel methodology and discuss how it can be used for the high-yielding one-pot intermolecular coupling of differentially protected cysteine thiols to afford unsymmetrical cystine derivatives as a model reaction for intermolecular peptide disulfide heterodimer synthesis.

2. Results and discussion

Our new reaction was discovered while investigating the potential of BtCl as an alternative to *N*-chlorosuccinimide[21] (NCS) in the context of unsymmetrical disulfide synthesis. Thus, reaction of *p*-methoxybenzenethiol as a representative thiol at −78 °C with BtCl (1.5 equiv) in DCM for 2 h led to two more polar (relative to the thiol) closely running product spots on TLC that were later separated and identified by ^1H NMR spectroscopy as the two

This in situ trapping contrasts with the equivalent case using NCS[21] in which the succinimide by-product is not nucleophilic enough to trap out the sulfenyl chloride formed unless a base like triethylamine is added, by which time significant homodimer 1 has formed. The R^1SBt derivative could be isolated by flash column chromatography but rapidly degraded over time in solution, and is thus better suited to a one-pot procedure. Thus, keeping it in solution and reacting it at −20 °C with a second thiol as *n*-PrSH[19] (1.5 equiv) resulted in rapid (30 min) nucleophilic substitution to afford the desired unsymmetrical disulfide in 67% isolated yield after chromatography (Scheme 3).



Scheme 3. Coupling of R^2SH with sulfenyl derivative R^1SBt.

Based on this mechanistic understanding, it was found that the presence of BtH (1 equiv) in the reaction improved the yield from 67 to 91% by promoting the in situ trapping reaction of R^1SCl in preference to homodimerisation via reaction of R^1SCl with R^1SH. BtH was superior to other additives evaluated such as thiourea (41%) and triethylamine (18%). With added BtH (1 equiv), the nature of the leaving group in the second substitution with R^2SH is open to speculation since the R^1SBt intermediates shown in Scheme 3 may be converted via their HCl salts, or alternatively via neutral forms following exchange with the added BtH. Thereafter, the optimal reagent stoichiometries as well as the temperatures of the various steps were further optimized, and results for these studies are shown in Tables 1 and 2, respectively.

Table 1
Optimization of reagent stoichiometries of the BtCl coupling reaction

Entry	Number of equivalents				
	BtCl	BtH	R^1SH[a]	R^2SH[b]	yield[c] (%)
1	1.5	0	1	1.5	67
2	1	1	1	1	72
3	1	1	1	1.5	73
4	1.5	1	1	1	72
5	1.5	1	1	1.5	91

[a] *p*-Methoxybenzenethiol; 2 h at −78 °C.
[b] 1-Propanethiol, 30 min at −20 °C.
[c] After work-up and column chromatography.

As observed in Tables 1 and 2, the optimized conditions turned out to be the addition of R^1SH (1 equiv) to BtCl (1.5 equiv) with BtH (1 equiv) in DCM at −78 °C, stirring for two hours at −78 °C

Table 2
Optimization of temperature of thiol additions[a]

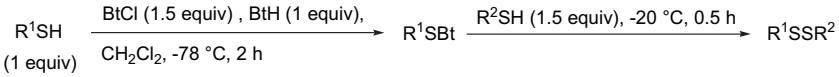
Entry	Temperature (°C) of addition		Yield[d] (%)	
	R^1SH[b]	R^2SH[c]	R^1SSR^1	R^1SSR^2
1	0	[e]	70	—
2	−20	−20	25	70
3	−78	−20	Trace[f]	91
4	−78	−78	—	93

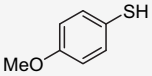
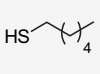
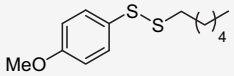
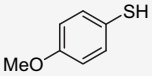
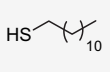
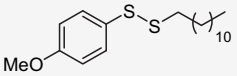
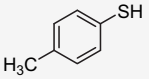
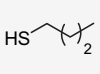
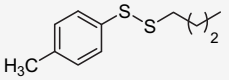
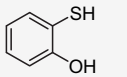
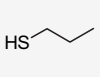
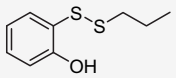
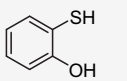
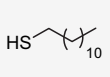
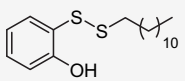
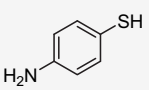
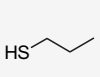
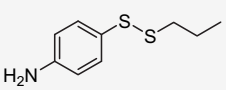
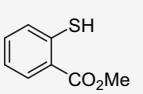
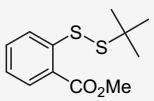
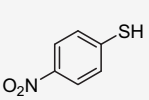
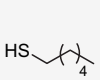
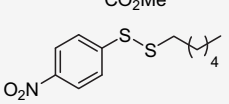
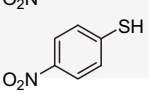
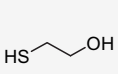
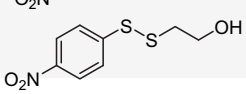
[a] Times as for Table 1.
[b] *p*-Methoxybenzenethiol.
[c] 1-Propanethiol.
[d] After work-up and chromatography.
[e] Not added.
[f] By TLC.

(shorter times may be possible), followed by the addition of R^2SH (1.5 equiv) at −78 °C or −20 °C and leaving for 30 min. For the full study it was decided to run the second step at −20 °C rather than at −78 °C in order to accommodate the range of substrates. At this temperature, complete substitution to afford the final product occurred within thirty minutes. These conditions were rigorously adhered to for the full-scale study (see Table 3), although it is recognized that some fine-tuning of time and temperature is possible between steps one and two. Of extreme significance was the observation that no homodimer 1 (or only traces) could be detected by TLC, indicating that interception of the sulfenyl chloride by BtH must be rapid, no doubt owing to the softness of the Bt anion preferring attack at sulfur rather than capturing a proton (Scheme 4).

With the minimization of formation of homodimer 1 accomplished, we had thus achieved our primary objective. A slight excess of BtCl (1.5 equiv) was needed to ensure the complete conversion of R^1SH as well as to minimize homodimer 1 formation, thus a matching excess of R^2SH was added to destroy the excess BtCl, inevitably resulting in some homodimer 2 being formed. According to mechanistic considerations from Schemes 1 and 2, an excess of 0.5 equiv of BtCl could result in the consumption of 1 equiv of R^2SH as 0.5 of the latter for reaction with the BtCl to form R^2SBt and 0.5 of it for reaction with R^2SBt to form R^2SSR^2, indicating the need to add 2 equiv of R^2SH overall in order to maximize the yield of R^1SSR^2. However, the finding that the yield of R^1SSR^2 in the model study using 1.5 equiv of R^2SH was up to 93% with complete consumption of R^1SBt led us to keep the amount of BtCl at 1.5 equiv throughout the broader study. The work-up involved an extraction using aqueous basic sodium thiosulfate to remove any traces of BtCl as well as HCl, which, following evaporation of solvent in the normal fashion furnished a residue that could be chromatographically separated into homodisulfide, heterodisulfide and BtH. However, as mentioned previously,[19] one could alternatively use an acid-base extraction to recover the BtH separately, which is something that holds promise for large-scale work. In such a way, we thus consider our new methodology to have a degree of greenness in view of the fact that BtCl is prepared from BtH (recoverable) and bleach as a benign oxidant. Overall therefore, it was decided to take these conditions as optimal in which homodimer 1 formation was avoided but at the expense of forming some homodimer 2. The full ramifications of this once we broadened the categories of thiol led

Table 3
BtCl Methodology for aromatic–aliphatic disulfide synthesis



Entry	R^1SH	R^2SH	R^1SSR^2	Yield (%)
1				80
2				92
3				81
4				80
5				91
6				64
7				90
8				84
9				76

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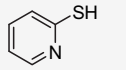
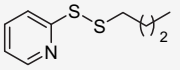
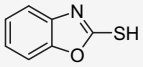
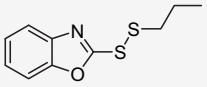
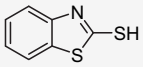
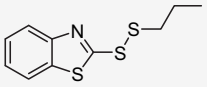
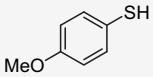
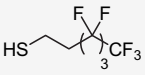
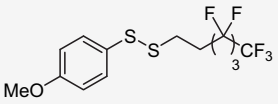
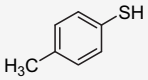
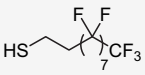
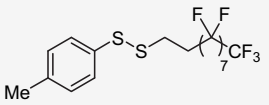
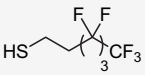
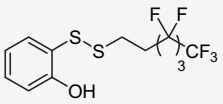
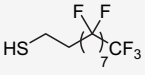
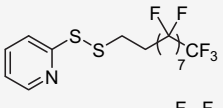
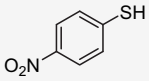
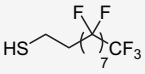
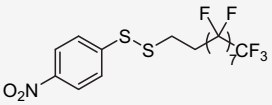
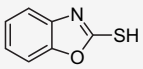
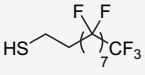
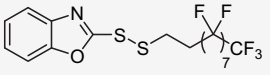
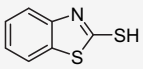
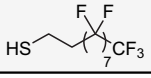
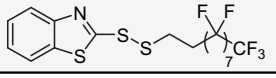
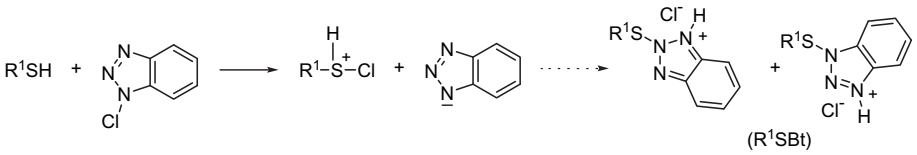
10				87
11				92
12				90
13				54
14				66
15				64
16				60
17				62
18				55
19				59



Scheme 4. Mechanism of R^1SBt formation.

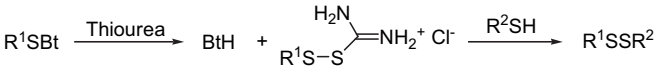
us to fine-tune the method into a variation for cases in which product and homodimer 2 could not be readily separated chromatographically. Finally, changing the solvent to THF had no detrimental effect on the reaction yield but carrying the reaction out in a water/THF mixture resulted in formation of homodimer 1 only, presumably via hydrolysis of the sulfenyl chloride, R^1SCl.

With a successful model reaction in place, attention was focused on exploring the various types of R groups of the two thiols, and from the outset we identified three groups of targets as aromatic–aliphatic, aromatic–aromatic and aliphatic–aliphatic, each with its own idiosyncrasies and in which aromatic would include hetero-aromatic. Our initial study identified that the aliphatic–aliphatic class was problematic because homodimer 2 could not be separated from the target unsymmetrical disulfide, and it was thus decided to modify the method for this class of disulfide, which will be described as a separate category. However, generally for the aromatic–aliphatic and aromatic–aromatic classes we have found that the methodology works very well and that the product is usually separable from homodimer 2 using conventional silica-gel chromatography. Importantly, the high yields and negligible amounts of homodimer 1 formed indicate that exchange reactions between heterodisulfide and R^2SH or between disulfides is negligible post-coupling, which can be a serious problem with other methodologies particularly in the case of aromatic–aromatic disulfide synthesis. Yields for the two classes tended to be above 80% with homodimer 1 formation as generally negligible. We have screened a large number of variants incorporating various functionalities and chain lengths expanding on our earlier results. Table 3 covers the aromatic–aliphatic cases. All examples are ones not previously reported by us and fourteen of the nineteen products in Table 3 are new compounds.

Some aspects of the results in Table 3 merit discussion. As reported previously, the preferred order of addition for the aromatic–aliphatic cases involved adding the aromatic thiol as R^1SH first in view of the high reactivity of alkylsulfenyl chlorides, which resulted in some homodimer 1 formation when adding the aliphatic thiol first as R^1SH. The aromatic–aliphatic cases proved to be compatible with a range of substrate characteristics to include

both electron-releasing (entries **1**–**6**), and electron-withdrawing (entries **7**–**12**) substituents in the aromatic ring, varied length of alkyl chain, steric bulk around the disulfide bond (entry **7**), as well as unprotected functionality in either thiol partner (entries **4**, **6** and **9**) as a useful feature for synthesizing functionalised disulfides for further elaboration. Electron-deficient heteroaromatic rings also worked well in the reaction, and both the pyridyl (entry **10**) and benzothiazolyl (entry **12**) products offer possibilities as precursors for exchange reactions with other thiols for accessing other unsymmetrical disulfides. A small library of fluoroalkyl aryl disulfides (entries **13**–**19**) were also prepared as potential precursors for garlic allicin mimics,[22] following a report by Brace[23] that fluorine substitution in the allicin chain enhanced thiosulfinate stability. Their chemoselective oxidation gave a family of aryl fluoroalkylthiosulfinates, whose stability and *anti*-microbial activity will be reported elsewhere. The C-10 fluorinated thiol used as R^2SH was obtained commercially, while the C-6 substrate was obtained from its iodide via thiourea methodology. In view of its volatility, the C-6 thiol was used directly as R^2SH in the BtCl reaction in a methanol/DCM medium following the breakdown of the isothiouronium salt in KOH in methanol. This led to the interesting observation that the BtCl methodology is compatible with methanol in the second step once R^1SBt has formed, even though the first step is not compatible with protic solvents in view of the intermediacy of a sulfenyl chloride. The yields for the family of fluorinated disulfides (entries **13**–**19**) were generally lower than the other cases at around the 60% mark and the products displayed typically fluorous physical characteristics such as dubious homogeneous solubility in standard organic solvents making them a little difficult to manipulate and contributing to the lower yield following chromatography. Characterisation[24] of the fluoroalkyl aryl disulfides was mainly provided by NMR (^1H, ^{13}C and ^{19}F) spectroscopy, which gave rise to some interesting characteristics. Thus, only the hydrogen-bearing carbons could be discerned for the aliphatic carbons of the R^2 group chain in the ^{13}C spectra, with fluorinated carbons being too relaxed to be observed. Carbon 2 on the chain vicinal to the first fluorinated carbon, as expected appeared as a triplet due to C–F coupling ($J \approx 22$ Hz). Similarly, their ^{19}F spectra gave highly coupled resonances for sets of fluorines on individual carbons covering a range from −82 ppm for the trifluoromethyl fluorines to −125 ppm for the internal difluorinated pairs in accordance with assignments by Brace.[23] By comparison, their analytical data proved to be elusive in that the fluorinated disulfides that were solids following chromatography could only be recrystallized from trifluoroethanol, which resulted in decomposition as evidenced by ^1H NMR and TLC of the products formed. The fluorinated disulfides could be carefully chromatographed to an acceptable level of purity sufficient to secure an acceptable CHN analysis, but such solids when subjected to a melting point determination on a hot-stage microscope gave different melting points due to polymorphic forms.

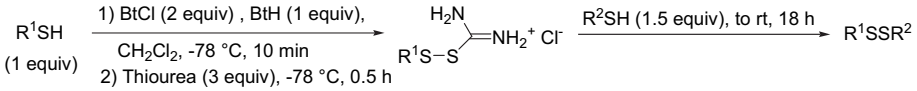
The application of the methodology to the formation of aliphatic–aliphatic disulfides encountered problems in that the desired heterodimer disulfide generally could not be separated from homodimer 2 in view of the non-polar nature of the thiols used. It is reasonable to surmise that this has been a general problem throughout the literature in the preparation of this class of molecule when dealing with labile R^1SLG intermediates, and that products of this nature reported using such methodologies have been obtained in varying degrees of purity. It was also evident from TLC studies, that an aliphatic thiol reacts with BtCl faster than an aromatic one and that a degree of homodimer 1 may be formed. The latter complication was rectified by increasing the equivalents of BtCl used from 1.5 to two, which effectively eliminated formation of homodimer 1 by increasing the rate of thiol conversion to sulfenyl chloride. Thereafter, the solution to the problem of homodimer 2 formation was solved by the addition of thiourea (3 equiv) at low temperature (−78 °C), once R^1SBt formation was complete (10–20 min), resulting in the destruction of excess BtCl, presumably with oxidation of thiourea to its disulfide. R^2SH was then added (3 equiv) and the solution left to warm to room temperature overnight. Longer reaction times were required in order to secure a high yield of R^1SSR^2, suggesting that R^1SBt is transformed by thiourea into an isothiouronium salt, a class of sulfenyl derivative that has been previously described[10] in the context of disulfide synthesis (Scheme 5).

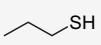
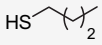
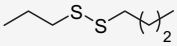
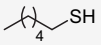
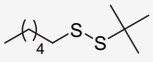
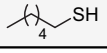
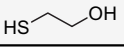
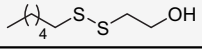


Scheme 5. Modified BtCl methodology for aliphatic–aliphatic disulfides.

No work-up in the modified reaction was required and excess R^2SH could be removed on the rotoevaporator along with reaction solvent. Chromatography of the residue furnished a pure product (entries **20**–**22**). Table 4 depicts three new representative examples, while Figures 1 and 2 depict the ^1H NMR spectra of samples of *tert*-butyl propyl disulfide[19] obtained via the normal BtCl and modified (thiourea) BtCl methods, respectively, in which *n*-PrSH was added as R^1SH. The spectra clearly show the superior purity (~60:40 to 100%) of the material obtained from the modified methodology.

Table 4
Modified BtCl methodology for aliphatic–aliphatic R^1SSR^2



Entry	R^1SH	R^2SH	R^1SSR^2	Yield (%)
20				94
21				94
22				76

The yields of the heterodimer disulfides were mostly excellent at above 80%, except for the anomalous entries of **28a–d** involving *p*-tolylthiol. Yields were not related to the degree of activation or deactivation in the aromatic rings, thus activated–activated (entry

In the final group, various new combinations of aromatic and heteroaromatic rings were studied for producing aromatic–aromatic disulfides[25] covering electron-withdrawing, electron-releasing, and heteroaromatic ring systems (entries **23**–**28**, Table 5). Varying the order of thiol addition as well as the temperature in the second step with R^2SH were also studied.

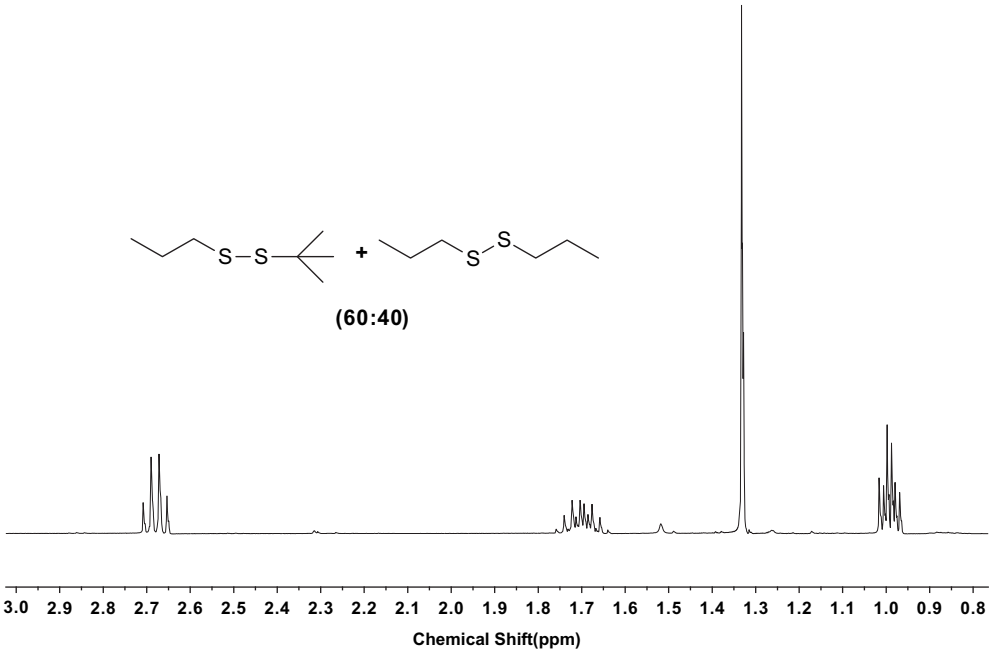


Figure 1. ^{1}H NMR spectrum of a 60:40 mixture of *tert*-butyl propyl disulfide[19] and dipropyl disulfide (homodimer 1) obtained (after chromatography) using the BtCl method.

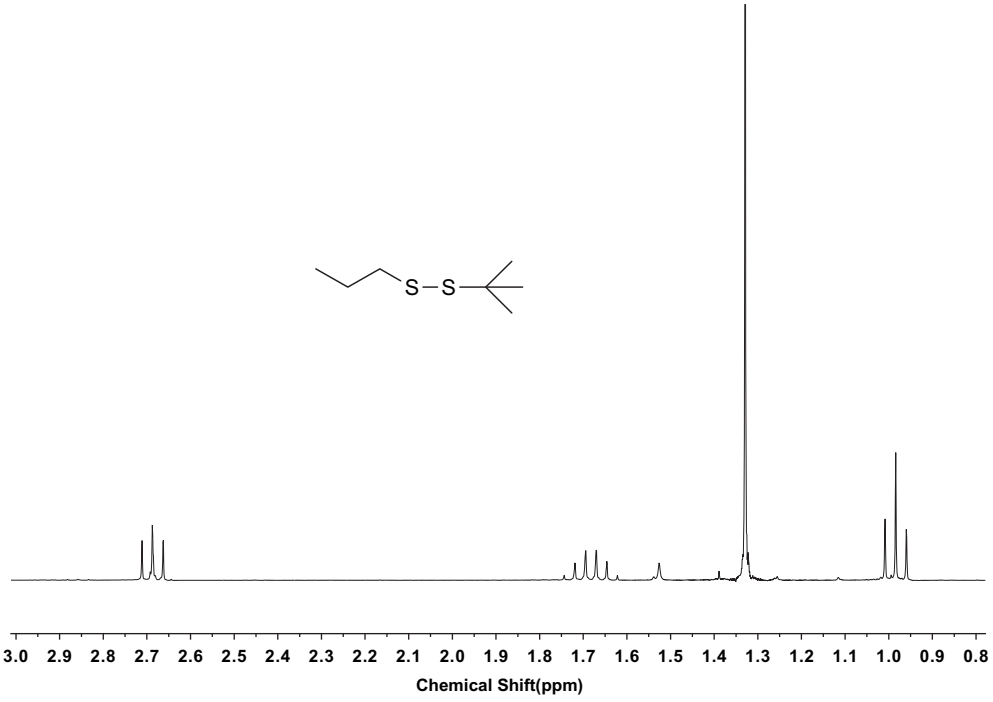
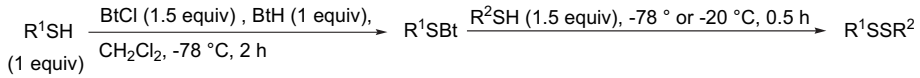


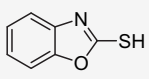
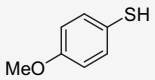
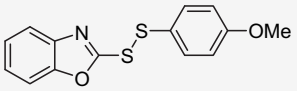
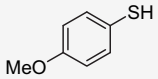
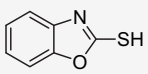
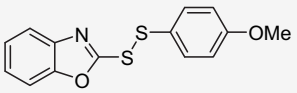
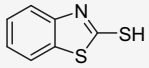
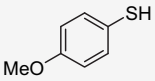
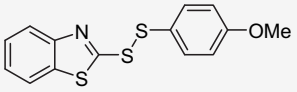
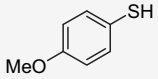
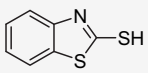
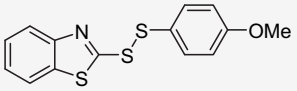
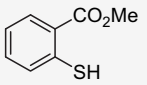
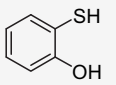
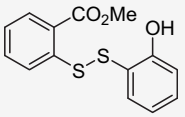
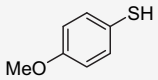
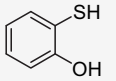
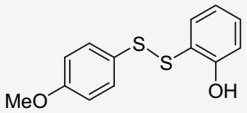
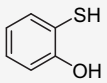
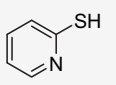
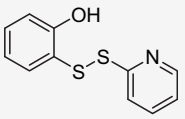
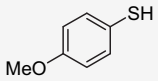
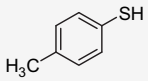
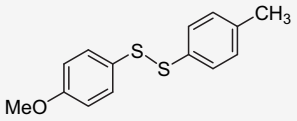
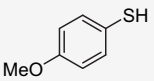
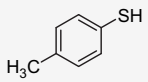
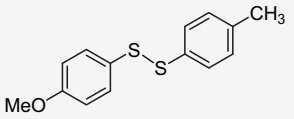
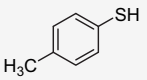
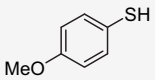
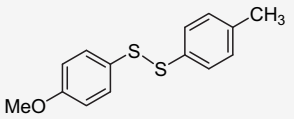
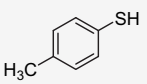
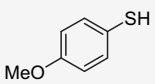
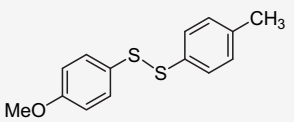
Figure 2. ^{1}H NMR spectrum of pure *tert*-butyl propyl disulfide obtained using the modified BtCl method.

26) and activated–deactivated (entries **25**, **27**) targets were prepared in high yields, while a deactivated–deactivated case (salicyl–pyridyl) had been reported previously by us.[19] An issue mentioned previously was the influence of the order of thiol addition, but generally this turned out to be inconsequential. For instance, for entries **23a**,**b** and **24a**,**b** involving benzoxazole-2-thiol and benzothiazole-2-thiol, respectively with *p*-anisylthiol, the yield within experimental error was independent of the mode of addition. Lowering the temperature in the addition of R^2SH from −20 °C to −78 °C also had no effect in this case. Significantly, as discussed later, no homodimer 1 due to exchange was detected either at the end of the reaction or after the chromatographic separation. One limitation noted, however, was the failure to couple the two heteroaromatic thiols from entries **23** and **24**. Since we had noted irregularities previously[19] with *p*-tolylthiol on the issue of addition order, the various combinations of its reaction with *p*-anisylthiol were studied. As the entries in **28a**–**d** reveal, yields were lower at −20 °C compared to those at −78 °C by about 15–20% indicating that this is one case that warrants the lower temperature in the second addition step. However, there was no evidence of the overall yield being affected by addition order, although this was the one case in which some degree of exchange was detected.

The issue of studying exchange reactions post-coupling involving the product heterodimer was addressed in the following way. R^1SH is totally consumed in the first step by virtue of the addition of excess BtCl, and homodimer 1 (R^1SSR^1) was not

Table 5
BtCl methodology for aromatic–aromatic disulfide synthesis



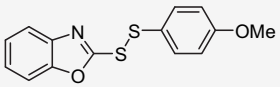
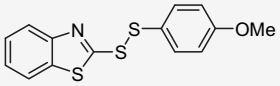
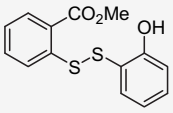
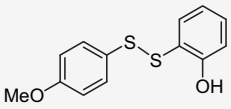
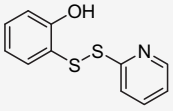
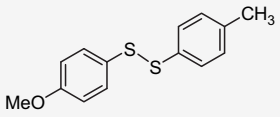
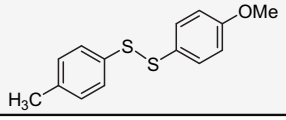
Entry	R^1SH	R^2SH	Temp °C[a]	R^1SSR^2	Yield (%)
23a			−20		88
23b			−78		86
24a			−20		91
24b			−78		85
25			−20		86
26			−20		84
27			−20		95
28a			−20		59
28b			−78		75
28c			−20		58
28d			−78		79

[a] For step 2 with R^2SH.

detected at the end of step 1 by TLC in any of the cases studied. Since R^2SH is then added in excess with inevitable formation of homodimer 2, the possibility of exchange on the unsymmetrical disulfide by R^2SH was addressed by TLC monitoring for the regeneration of R^1SH and formation of homodisulfide 1 via exchange of any such R^1SH with the heterodimer at the end of the reaction period. Alternatively, two molecules of heterodimer could disproportionate also to give homodimer 1. In addition to TLC monitoring, all products eluting from the column were exhaustively scrutinised by ^1H NMR spectroscopy. The results are shown in Table 6.

In no cases was R^1SH detected at any stage (TLC or column) and R^1SSR^1 was only detected (and isolated) in one case after work-up involving the intriguingly troublesome *p*-tolylthiol in the entries of **28**. For the latter, at the lower temperature of −78 °C (see entries **28b**,**d** in Table 6), homodimer 1 could be detected after work-up and isolated in 10% after chromatography. This explains the lower yields of heterodimer disulfide for entries **28a**,**c** in Table 5 at the higher temperature (−20 °C) presumably as a result of a greater degree of exchange. Furthermore, the results indicate the exchange to occur late in the reaction profile presumably as a result of

Table 6
Analysis on disulfide exchange for reactions in Table 5

Entry & Yield[a] (%)	Product	Homodimer 1 (after step 1 by TLC)	Homodimer 1 (after step 2 by TLC)	Homodimer 1[a] (after work-up and chromatography)
23b (86%)		No	No	No
24b (85%)		No	No	No
25 (86%)		No	No	No
26 (84%)		No	No	No
27a (95%)		No	No	No
28b (75%)		No	No	Yes (10%)
28d (79%)		No	No	Yes (10%)

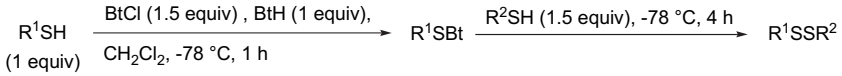
[a] Yields after column chromatography.

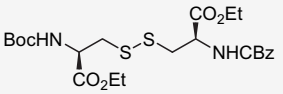
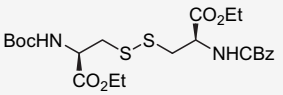
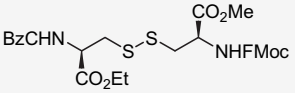
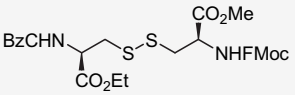
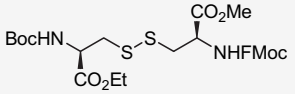
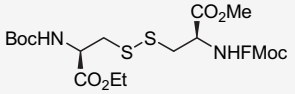
warming of the solution towards the work-up phase. The generally promising outlook of minimal disulfide exchange for aromatic–aromatic products undoubtedly reflects the low temperatures involved in the coupling, which for aromatic–aromatic coupling is preferred as −78 °C for both addition steps. All disulfide products returned acceptable microanalytical or correct HRMS data in addition to appropriate NMR data.

In the final part of the study, it was decided to extend our work on unsymmetrical cysteine disulfides. Earlier work by us[26] had identified that both aliphatic and aromatic cysteine disulfides could be prepared in good yield and in one-pot by the standard BtCl methodology (−20 °C for the R^2SH addition step). We thus decided to extend the study to coupling protected cysteine thiols, since the intermolecular synthesis of peptide disulfide heterodimers continues to be a challenge. Approaches are known for unsymmetrical cystine models,[27] with a recent interesting aqueous variant using sulfenyl thiocyanates,[5c] as well as both solution[28] and solid-phase intermolecular couplings.[29] However, in each case the usual prior activation of one of the thiols, with the nitropyridylthio group being invariably the activator of choice,[30] has been an obligatory step in the sequence. Consequently, as a step towards developing the BtCl methodology for a one-pot peptide disulfide heterodimer synthesis via intermolecular thiol coupling, we decided to study the synthesis of unsymmetrical cystine derivatives as a model with orthogonal variation of the *N*-protecting groups as the FMoc, Boc and CBz standards and varying the carboxyl as methyl or ethyl ester. The objective that we were thus interested in achieving was to accomplish activation and coupling in a one-pot reaction while maintaining a high yield. The cysteine precursors with *N*-Boc and *N*-CBz could be prepared in high yield by reaction of cysteine ester hydrochloride with $(Boc)_2O$ or CBzCl using a slurry of $NaHCO_3$ as base in CH_2Cl_2 overnight at room temperature. Exclusive N-protection was observed and this provided a useful alternative to published methods.[31] Similarly, the FMoc cysteine derivative could be prepared from commercially available *S*-trityl-FMoc-cysteine via a known two-step procedure involving esterification[32] (CH_3COCl/MeOH) and trityl deprotection[33] (Et_3SiH/CF_3CO_2H). All starting materials returned data consistent with literature values including correct $[\alpha]_D^{20}$ values where reported in the literature. Earlier work by us[26] on the aralkyl cysteine disulfides had established that the order of thiol addition affected the reaction outcome in that triethylamine needed to be present when adding the cysteine thiol second in order to avoid Boc hydrolysis. Conversely, when adding the cysteine thiol first, no triethylamine was required as the overall conversion could be conducted at a lower temperature. Bearing all this in mind, it was decided in the first instance to retain the standard conditions from Table 3 with -20 °C for the addition of R^2SH, and to do reactions separately with and without triethylamine. The overall results turned out to be disappointing, returning products for either case in low yield around the 40% mark after chromatography. Analysis of the by-products alluded to the possibility of *N*-protecting group participation with SBt or the disulfide product moiety. In view of the high reactivity of aliphatic thiols under the standard BtCl conditions, it was decided to lower the temperature in the second thiol addition step to −78 °C and to omit triethylamine. Thus, the conditions became simply to add the cysteine derivative R^1SH (1 equiv) to BtCl (1.5 equiv) with BtH (1 equiv) at −78 °C in CH_2Cl_2, leave for 1 h and then add cysteine derivative R^2SH (1.5 equiv) at the same temperature. Reactions were then left to stir at −78 °C for four hours before being

quenched in the normal way (aq $Na_2S_2O_3/NaHCO_3$). To our delight, following chromatographic purification, the desired unsymmetrical cystine derivatives were all obtained as new compounds in high yields of around 90% and in which the yield was independent of either the choice of protecting group or order of cysteine thiol addition. ^1H and ^{13}C NMR spectroscopic analysis suggested a stereochemically homogeneous disulfide product in each case with no indication of epimerization, consistent with the mild conditions of temperature and basicity. This conclusion was supported by HPLC results, which showed a single disulfide product peak in each case (see Supplementary data). The results are shown in Table 7. These findings bode well for the possibility of synthesizing larger peptide disulfide heterodimers via intermolecular coupling and in a one-pot fashion that avoids the use of a separate activation step.

Table 7
Coupling of N-protected cysteines via BtCl methodology



Entry	R^1SH	R^2SH	R^1SSR^2	Yield (%)
29a	*N*-Boc-L-Cys Et Ester	*N*-CBz-L-Cys Et Ester		91
29b	*N*-CBz-L-Cys Et Ester	*N*-Boc-L-Cys Et Ester		89
30a	*N*-CBz-L-Cys Et Ester	*N*-FMoc-L-Cys Me Ester		91
30b	*N*-FMoc-L-Cys Me Ester	*N*-CBz-L-Cys Et Ester		89
31a	*N*-Boc-L-Cys Et Ester	*N*-FMoc-L-Cys Me Ester		90
31b	*N*-FMoc-L-Cys Me Ester	*N*-Boc-L-Cys Et Ester		90

In conclusion, the chemistry of 1-chlorobenzotriazole has opened up a new methodological option for the efficient and facile one-pot synthesis of various classes of unsymmetrical disulfides. We are continuing to develop the methodology to accessing the unsymmetrical disulfides of other biomolecules and the results on this will be reported in due course.

3. Experimental section

3.1. General

Thin layer chromatography (TLC) was used to monitor reactions using aluminium-backed plates coated with silica-gel F_{254}. Compounds on TLC plates were observed by a combination of ultra-violet light, iodine vapour, or by spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v) and then heating at 150 °C. Column chromatography was performed using silica-gel 60 mesh. All chromatography was carried out using either petroleum ether (bp 40–60 °C) or ethyl acetate as eluents, or a combination of these. The HPLC analysis of the cystine derivatives was carried out using a Thermo Separation Products (TSP) HPLC system (Spectra SERIES P200) consisting of a manual injection port (20 μL loop) attached to a Spectra SERIES P200 UV 150 detector set at 220 nm. The column used was a Phenomenex® Luna 5 μm C18(2), 150 mm×4.6 mm (Phenomenex, UK). The temperature of the column was kept constant at room temperature (18–20 °C). Delta Chromatography Software (Delta 5.0) was used for instrument control and data acquisition. The mobile phase composition was acetonitrile/water (35:65) at a flow rate of 1.0 mL min^{-1}. Samples were dissolved in the mobile phase and 20 μL samples were injected into the HPLC system at room temperature (18–20 °C). Acetonitrile was HPLC grade and Milli-Q water was used. Solvent systems and sample solutions were degassed before use. Optical rotations were obtained using a Perkin Elmer 343 polarimeter at 20 °C. The concentration *c* refers to g/100 mL. Melting points were measured on a hot-stage microscope. Infrared spectra were recorded in chloroform, dichloromethane or neat on caesium chloride or sodium chloride plates on an FTIR spectrophotometer. Elemental analyses were performed using a CHN elemental analyser. High resolution mass spectrometry data was obtained using a micromass spectrometer. ^1H and ^{13}C NMR spectra were recorded at 300 MHz for ^1H and 75.5 MHz for ^{13}C or at 400 MHz for ^1H and 100.6 MHz for ^{13}C in deuteriochloroform ($CDCl_3$) unless otherwise stated. Chemical shifts are quoted using residual chloroform (δ 7.24 in ^1H NMR and δ 77.00 in ^{13}C NMR) as an internal standard. All chemical shifts are reported in parts per million and all coupling constants are quoted in hertz. All chemicals and reagents were commercially available, except 3,3,4,4,5,5,6,6,6-nonafluoro-1-hexanethiol, which was prepared from reaction of 1,1,1,2,2,3,3,4,4-nonafluoro-6-iodohexane with thiourea, as well as the intermediates for synthesis of the cystine derivatives, which are referenced in the experimental section. All solvents were purified using standard methods and freshly distilled before use.

3.2. General procedure for aromatic–aliphatic disulfides as illustrated for entry 1 in Table 3

To a stirred solution of 1-chlorobenzotriazole (0.61 g, 4.0 mmol) and benzotriazole (0.32 g, 2.7 mmol) in CH_2Cl_2 (20 mL) under N_2 at −78 °C was added dropwise a solution of *p*-methoxybenzenethiol as R^1SH (0.37 g, 2.7 mmol) dissolved in CH_2Cl_2 (2 mL) and the solution was allowed to stir for 2 h. 1-Hexanethiol as R^2SH (0.47 g, 4.0 mmol) in CH_2Cl_2 (2 mL) was then added slowly at −20 °C. The reaction was left stirring for 30 min before being quenched with an aqueous solution of $Na_2S_2O_3$ (0.50 g in 10 mL water) together with saturated aqueous $NaHCO_3$ (20 mL), followed by rapid stirring at 0 °C for 20 min and extraction with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica-gel column chromatography using petroleum ether/ethyl acetate mixtures to afford 1-hexyl 4-methoxyphenyl disulfide (entry 1.055 g, 2.16 mmol, 80%) as a pale-yellow oil. IR (CH_2Cl_2): ν_{max} 495 cm^{-1} (S–S); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.48 (2H, d, *J*=8.8 Hz), 6.86 (2H, d, *J*=8.8 Hz), 3.80 (3H, s), 2.73 (2H, t, *J*=7.1 Hz), 1.66 (2H, quint, *J*=7.1 Hz), 1.34 (2H, m), 1.26 (4H, m), 0.87 (3H, t, *J*=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 159.5, 131.6, 128.6, 114.6, 55.4, 38.9, 31.4 28.7 28.1, 22.5, 14.0; HRMS (EI) *m*/*z* calcd (M^+) for $C_{13}H_{20}OS_2$ 256.0956, found 256.0949.

3.3. General procedure for aliphatic–aliphatic disulfides as illustrated for entry 20 in Table 4

To a stirred solution of 1-chlorobenzotriazole (0.61 g, 4.0 mmol) and benzotriazole (0.24 g, 2.0 mmol) in CH_2Cl_2 (20 mL) under N_2 at −78 °C was added dropwise a solution of 1-propanethiol as R^1SH (0.15 g, 2.0 mmol) in CH_2Cl_2 (2 mL). After 10 min, a solution of thiourea (0.46 g, 6.0 mmol) dissolved in dry THF (5 mL) was added and the solution stirred for a further 10 min. 1-Butanethiol as R^2SH (0.27 g, 3.0 mmol) in CH_2Cl_2 (2 mL) was added slowly at −78 °C and the solution stirred for 18 h with slow warming to room temperature. The solvent was evaporated under reduced pressure and the crude material was purified directly by silica-gel column chromatography using petroleum ether/ethyl acetate mixtures to afford 1-butyl 1-propyl disulfide (entry **20**, 0.31 g, 1.87 mmol, 94%) as a clear-yellow oil; IR (CH_2Cl_2): ν_{max} 476 (S–S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 2.64 (4H, m), 1.65 (4H, m), 1.38 (2H, sext, *J*=7.4 Hz), 0.96 (3H, t, *J*=7.4 Hz), 0.89 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 41.2, 38.9, 31.3, 22.5, 21.6, 13.7, 13.1; HRMS (EI) *m*/*z* calcd (M^+) for $C_7H_{16}S_2$ 164.0693, found 164.0688.

3.4. Procedure for aromatic–aromatic disulfides as illustrated for entry 23a in Table 5

To a stirred solution of 1-chlorobenzotriazole (0.61 g, 4.0 mmol) and benzotriazole (0.32 g, 2.7 mmol) in CH_2Cl_2 (20 mL) under N_2 at −78 °C was added dropwise a solution of benzoxazole-2-thiol as R^1SH (0.41 g, 2.7 mmol) dissolved in CH_2Cl_2 (2 mL) and the solution was allowed to stir for 2 h. *p*-Methoxybenzenethiol as R^2SH (0.56 g, 4.0 mmol) in CH_2Cl_2 (2 mL) was then added slowly at −78 °C (or at −20 °C according to Table 5). The reaction was left stirring for 30 min before being quenched with an aqueous solution of $Na_2S_2O_3$ (0.50 g in 10 mL water) together with saturated aqueous $NaHCO_3$ (20 mL), followed by rapid stirring at 0 °C for 20 min and extraction with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica-gel column chromatography using petroleum ether/ethyl acetate mixtures to afford 2-benzoxazolyl *p*-methoxyphenyl disulfide (entry **23a**, 0.69 g, 2.38 mmol, 88%) as a yellow oil. IR (CH_2Cl_2): ν_{max} 500 (S–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.68 (3H, m), 7.49 (1H, m), 7.31 (2H, m), 6.86 (2H, d, *J*=9.0 Hz), 3.78 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 161.0, 161.0, 152.4, 141.9, 134.7, 132.0, 124.7, 124.6, 119.4, 114.9, 110.3, 55.3; HRMS (ESI) *m*/*z* calcd (M^++H) for $C_{14}H_{12}NO_2S_2$ 290.0309, found 290.0300.

3.5. General procedure for cystine disulfides as illustrated for entry 29a in Table 7

To a stirred solution of 1-chlorobenzotriazole (0.115 g, 0.75 mmol) and benzotriazole (0.060 g, 0.50 mmol) in CH_2Cl_2 (5 mL) under N_2 at −78 °C was added dropwise a solution of *N*-*tert*-butoxycarbonyl-L-cysteine ethyl ester as R^1SH (0.124 g, 0.50 mmol) dissolved in CH_2Cl_2 (1 mL). The solution was allowed to stir for 2 h at −78 °C. *N*-Benzyloxycarbonyl-L-cysteine ethyl ester as R^2SH (0.213 g, 0.75 mmol) in CH_2Cl_2 (1 mL) was then added slowly at −78 °C and the solution stirred for 4 h. The reaction was then quenched with a solution of $Na_2S_2O_3$ (0.20 g in 5 mL of water) together with saturated aqueous $NaHCO_3$ (10 mL), followed by rapid stirring at 0 °C for 20 min and extraction with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica-gel column chromatography using petroleum ether/ethyl acetate mixtures to afford *N*-Boc-, *N*-CBz-L-cysteine diethyl ester (entry **29a**, 0.241 g, 0.455 mmol, 91%) as a clear sticky oil. $[\alpha]_D^{20}$ +39.4 (c 1.0, $CHCl_3$); IR (CH_2Cl_2): ν_{max} 3354 (NH), 1715 (C=O), 464 (S–S) cm^{-1}; HPLC T_R=9.12 min (the HPLC chromatogram can be found in the Supplementary data); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 (5H, m), 5.71 (1H, br s), 5.39 (1H, br s), 5.14 (2H, s), 4.65 (1H, br s), 4.58 (1H, br s), 4.22 (4H, m), 3.21 (2H, m), 3.15 (2H, m), 1.45 (9H, s), 1.29 (6H, t, *J*=7.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 170.5, 170.2, 155.6, 154.9, 136.1, 128.4, 128.1, 128.0, 80.1, 67.0, 61.9, 61.7, 53.4, 52.9, 41.3, 41.2, 28.2, 13.9, 13.9; HRMS (ESI) *m*/*z* calcd (M^++H) for $C_{23}H_{35}N_2O_8S_2$ 531.1835, found 531.1860.

3.6. Disulfides 1–28 from Tables 3–5

*3.6.1. Entry **1**: **1**-hexyl 4-methoxyphenyl disulfide.* Yield 0.553 g, 80%, as a pale-yellow oil; IR (CH_2Cl_2): ν_{max} 495 cm^{-1} (S–S); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.48 (2H, d, *J*=8.8 Hz), 6.86 (2H, d, *J*=8.8 Hz), 3.80 (3H, s), 2.73 (2H, t, *J*=7.1 Hz), 1.66 (2H, quint, *J*=7.1 Hz), 1.34 (2H, m), 1.26 (4H, m), 0.87 (3H, t, *J*=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 159.5, 131.6, 128.6, 114.6, 55.4, 38.9, 31.4 28.7 28.1, 22.5, 14.0; HRMS (EI) *m*/*z* calcd (M^+) for $C_{13}H_{20}OS_2$ 256.0956, found 256.0949.

*3.6.2. Entry **2**: **1**-decyl 4-methoxyphenyl disulfide.* Yield 0.775 g, 92%, as pale-yellow oil; IR (CH_2Cl_2): ν_{max} 499 cm^{-1} (S–S); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.49 (2H, d, *J*=9.0 Hz), 6.87 (2H, d, *J*=9.0 Hz), 3.80 (3H, s), 2.74 (2H, t, *J*=7.4 Hz), 1.68 (2H, quint, *J*=7.4 Hz), 1.34 (2H, m), 1.27 (12H, m), 0.90 (3H, t, *J*=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 159.4, 131.5, 128.6, 114.6, 55.3, 38.9, 31.9, 29.5, 29.4, 29.3, 29.1, 28.7, 28.4, 22.6, 14.1; HRMS (EI) *m*/*z* calcd (M^+) for $C_{17}H_{28}OS_2$ 312.1582, found 312.1576.

*3.6.3. Entry **3**: **1**-butyl p-tolyl disulfide*[34]. Yield 0.464 g, 81%, as pale-yellow oil; IR (CH_2Cl_2): ν_{max} 487 cm^{-1} (S–S); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.46 (2H, d, *J*=8.4 Hz), 7.15 (2H, d, *J*=8.4 Hz), 2.76 (2H, t, *J*=7.4 Hz), 2.36 (3H, s), 1.68 (2H, quint, *J*=7.4 Hz), 1.42 (2H, sext, *J*=7.4 Hz), 0.92 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 136.9, 134.2, 129.7, 128.3, 38.6, 30.8, 21.6, 21.0, 13.6; HRMS (EI) *m*/*z* calcd (M^+) for $C_{11}H_{16}S_2$ 212.0693, found 212.0688.

*3.6.4. Entry **4**: **2**-hydroxyphenyl 1-propyl disulfide.* Yield 0.430 g, 80%, as a yellow oil; IR (CH_2Cl_2): ν_{max} 3500 (OH), 499 (S–S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.51 (1H, dd, *J*=7.7, 1.5 Hz), 7.30

(1H, ddd, J=8.3, 7.7, 1.5 Hz), 7.01 (1H, dd, J=8.3, 1.5 Hz), 6.89 (1H, td, J=7.7, 1.5 Hz), 6.42 (1H, br s), 2.77 (2H, t, J=7.3 Hz), 1.75 (2H, sext, J=7.3 Hz), 0.99 (3H, t, J=7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 156.6, 134.8, 131.9, 121.1, 120.8, 115.9, 40.4, 21.9, 13.0; HRMS (EI) m/z calcd (M^+) for $C_9H_{12}OS_2$ 200.0330, found 200.0325.

*3.6.5. Entry **5**: **1**-dodecyl 2-hydroxyphenyl disulfide.* Yield 0.802 g, 91%, as a yellow oil; IR (CH_2Cl_2): ν_{max} 3428 (OH), 500 (S–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.49 (1H, dd, J=7.5, 1.4 Hz), 7.30 (1H, ddd, J=8.2, 7.5, 1.4 Hz), 7.00 (1H, dd, J=8.2, 1.4 Hz), 6.88 (1H, td, J=7.5, 1.4 Hz), 6.38 (1H, br s), 2.76 (2H, t, J=7.4 Hz), 1.69 (2H, quint, J=7.3 Hz), 1.34 (2H, m), 1.26 (16H, m), 0.88 (3H, t, J=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 156.6, 134.9, 131.9, 121.1, 120.8, 115.9, 38.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.5, 28.4, 22.7, 14.1; HRMS (EI) m/z calcd (M^+) for $C_{18}H_{30}OS_2$ 326.1738, found 326.1746.

*3.6.6. Entry **6**: p-aminophenyl 1-propyl disulfide.* Yield 0.345 g, 64%, as a dark-coloured oil; IR ($CHCl_3$): ν_{max} 3370, 3209 (NH), 490 (S–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.35 (2H, d, J=8.4 Hz), 6.62 (2H, d, J=8.4 Hz), 3.70 (2H, br s), 2.71 (2H, t, J=7.4 Hz), 1.71 (2H, sext, J=7.4 Hz), 0.96 (3H, t, J=7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 146.7, 132.7, 125.5, 115.5, 40.7, 22.0, 13.1; HRMS (EI) m/z calcd (M^+) for $C_9H_{13}NS_2$ 199.0489, found 199.0482.

*3.6.7. Entry **7**: tert-butyl o-methoxycarbonylphenyl disulfide[35].* Yield 0.622 g, 90%, as a clear oil; IR ($CHCl_3$) ν_{max} 1708 (C=O), 487 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.22 (1H, dd, J=8.2 Hz and 1.3 Hz), 7.97 (1H, dd, J=8.2 Hz and 1.3 Hz), 7.49 (1H, ddd, J=8.2 Hz, 7.5 Hz and 1.3 Hz), 7.19 (1H, ddd, J=8.2 Hz, 7.5 Hz and 1.3 Hz), 3.94 (3H, s), 1.32 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 166.8, 143.0, 132.2, 131.1, 127.1, 126.4, 124.9, 52.1, 49.2, 30.0; HRMS (EI) m/z calcd (M^+) for $C_{12}H_{16}O_2S_2$ 256.0592, found 256.0597.

*3.6.8. Entry **8**: 1-hexyl p-nitrophenyl disulfide.* Yield 0.615 g, 84%, as a pale-yellow oil; IR (neat): ν_{max} 1515, 1340 (NO_2), 499 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.19 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz), 2.76 (2H, t, J=7.4 Hz), 1.65 (2H, quint, J=7.4 Hz), 1.40 (2H, quint, J=7.4 Hz), 1.28 (4H, m), 0.89 (3H, t, J=7.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 147.3, 146.1, 125.8, 124.0, 39.1, 31.3, 28.9, 28.1, 22.4, 13.9; HRMS (EI) m/z calcd (M^+) for $C_{12}H_{17}NO_2S_2$ 271.0701, found 271.0693.

*3.6.9. Entry **9**: 2-hydroxyethyl p-nitrophenyl disulfide.* Yield 0.474 g, 76%, as pale-yellow oil; IR (neat): ν_{max} 3359 (OH), 1513, 1340 (NO_2), 469 (S–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 8.14 (2H, d, J=9.0 Hz), 7.66 (2H, d, J=9.0 Hz), 3.85 (2H, t, J=5.9 Hz), 2.93 (2H, t, J=5.9 Hz), 2.59 (1H, br s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 146.5, 146.2, 125.9, 124.0, 60.0, 41.3; HRMS (EI) m/z calcd (M^+) for $C_8H_9NO_3S_2$ 231.0024, found 231.0018; CHN Found: C 41.48%, H 3.90%, N 6.02, S 27.80%; $C_8H_9NO_3S_2$ requires C 41.55%, H 3.92%, N 6.06%, S 27.72%.

*3.6.10. Entry **10**: 1-butyl 2-pyridyl disulfide[36].* Yield 0.468 g, 87%, as pale-yellow oil; IR ($CHCl_3$): ν_{max} 478 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.45 (1H, m), 7.73 (1H, m), 7.63 (1H, m), 7.06 (1H, m), 2.80 (2H, t, J=7.4 Hz), 1.68 (2H, quint, J=7.4 Hz), 1.42 (2H, sext, J=7.4 Hz), 0.90 (3H, t, J=7.4 Hz), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 160.7, 149.5, 136.8, 120.4, 119.5, 38.7, 30.9, 21.6, 13.5; HRMS (EI) m/z calcd (M^+) for $C_9H_{13}NS_2$ 199.0489, found 199.0493.

*3.6.11. Entry **11**: 2-benzoxazolyl 1-propyl disulfide.* Yield 0.560 g, 92%, as a colourless semi-solid; IR (CH_2Cl_2): ν_{max} 469 (S–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.67 (1H, m), 7.48 (1H, m), 7.30 (2H, m), 2.97 (2H, t, J=7.2 Hz), 1.80 (2H, sext, J=7.2 Hz), 1.02 (3H, t, J=7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 163.6, 152.4, 142.0, 124.7, 124.5, 119.3, 110.2, 41.3, 22.0, 12.9; HRMS (ESI) m/z calcd (M^++H) for $C_{10}H_{12}NOS_2$ 226.0360, found 226.0352.

*3.6.12. Entry **12**: 2-benzothiazolyl 1-Propyl disulfide[37].* Yield 0.587 g, 90%, as a colourless semi-solid; IR (CH_2Cl_2): ν_{max} 500 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.88 (1H, dd, J=7.6, 1.2 Hz), 7.81 (1H, dd, J=7.6, 1.2 Hz), 7.44 (1H, td, J=7.6, 1.2 Hz), 7.34 (1H, td, J=7.6, 1.2 Hz), 2.96 (2H, t, J=7.3 Hz), 1.81 (2H, sext, J=7.3 Hz), 1.05 (3H, t, J=7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 173.2, 155.2, 135.9, 126.2, 124.5, 122.1, 121.1, 41.5, 22.4, 13.0; HRMS (ESI) m/z calcd (M^++H) for $C_{10}H_{12}NS_3$ 242.0132, found 242.0121.

*3.6.13. Entry **13**: p-methoxyphenyl 3,3,4,4,5,5,6,6,6-nonafluoro-1-hexyl disulfide.* Yield 0.609 g, 54%, as a clear oil; IR (CH_2Cl_2): ν_{max} 1265 (C–F), 499 (S–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.48 (2H, d, J=8.9 Hz), 6.88 (2H, d, J=8.9 Hz), 3.82 (3H, s), 2.89 (2H, m), 2.54 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 160.3, 132.9, 127.1, 114.9, 55.3, 31.4 (t, J_{C-F}=22.1 Hz), 28.5; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.5, −114.4 and −114.9, −124.8, −126.4; HRMS (EI) m/z calcd (M^+) for $C_{13}H_{11}F_9OS_2$ 418.0108, found 418.0103.

*3.6.14. Entry **14**: 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-1-decyl p-tolyl disulfide.* Yield 1.072 g, 66%, as a yellow solid; IR (CH_2Cl_2): ν_{max} 1265 (C–F), 499 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.45 (2H, d, J=8.0 Hz), 7.17 (2H, d, J=8.0 Hz), 2.91 (2H, m), 2.53 (2H, m), 2.37 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 138.1, 132.9, 130.0, 129.6, 31.5 (t, J_{C-F}=22.1 Hz), 28.8, 21.0; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.2, −114.2, −122.1, −122.3, −122.3, −123.1, −123.8, −126.5; HRMS (EI) m/z calcd (M^+) for $C_{17}H_{11}F_{17}S_2$ 602.0031, found 602.0022; Found: C 33.88%, H 1.89%, S 10.54%; $C_{17}H_{11}F_{17}S_2$ requires C 33.10%, H 1.84%, S 10.64%.

*3.6.15. Entry **15**: 3,3,4,4,5,5,6,6,6-nonafluorohexyl 2-hydroxyphenyl disulfide.* Yield 0.698 g, 64%, as a yellow solid; IR (CH_2Cl_2): ν_{max} 3472 (OH), 1265 (C–F), 499 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48 (1H, dd, J=7.6, 1.5 Hz), 7.36 (1H, ddd, J=8.4, 7.6, 1.5 Hz), 7.04 (1H, dd, J=8.4, 1.5 Hz), 6.92 (1H, td, J=7.6, 1.5 Hz), 6.24 (1H, br s), 2.96, (2H, m), 2.58 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 156.7, 135.0, 132.6, 121.1, 119.9, 116.3, 31.3 (t, J_{C-F}=22.1 Hz), 28.4; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.5, −114.5, −124.7, −126.4; HRMS (EI) m/z calcd (M^+) for $C_{12}H_9F_9OS_2$ 403.9951, found 403.9948.

*3.6.16. Entry **16**: 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-1-decyl 2-pyridyl disulfide[38].* Yield 0.955 g, 60%, as a colourless solid; mp (trifluoroethanol) 33–35 °C; IR (CH_2Cl_2): ν_{max} 1242 (C–F), 499 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.51 (1H, m) 7.65 (2H, m), 7.14 (1H, m), 3.04 (2H, m), 2.60 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 158.9, 150.0, 137.0, 121.2, 120.2, 31.6 (t, J_{C-F}=22.0 Hz), 29.3; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.2, −114.1, −122.1, −122.3, −122.3, −123.1, −123.8, −126.5; HRMS (ESI) m/z calcd (M^++H) for $C_{15}H_9F_{17}NS_2$ 589.9905, found 589.9982, Found: C 30.61%, H 1.36%, N 2.40%, S 10.99%; $C_{15}H_9F_{17}NS_2$ requires C 30.57%, H 1.37%, N 2.38%, S 10.88%.

*3.6.17. Entry **17**: 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-1-decyl p-nitrophenyl disulfide.* Yield 1.060 g, 62%, as a yellow solid; IR (CH_2Cl_2): ν_{max} 1520, 1342 (NO_2), 469 (S–S) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.22 (2H, d, J=9.0 Hz), 7.70 (2H, d, J=9.0 Hz), 2.98 (2H, m), 2.53 (2H, m, H-2′); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 146.7, 145.3, 126.4, 124.3, 31.5 (t, J_{C-F}=22.0 Hz), 29.2; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.2, −114.0, −122.0, −122.2, −122.2, −123.1, −123.6, −126.4; HRMS (ESI) m/z calcd (M^++H) for $C_{16}H_9F_{17}NO_2S_2$ 633.9803, found 633.9801.

*3.6.18. Entry **18**: 2-benzoxazolyl 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro-1-decyl disulfide.* Yield 0.935 g, 55%, as a colourless solid; IR (CH_2Cl_2): ν_{max} 1241 (C–F), 500 (S–S) cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$) δ_H: 7.67 (1H, m), 7.46 (1H, m), 7.30 (2H, m), 3.21 (2H, m), 2.67 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 162.4, 152.6, 141.8, 125.2, 124.8, 119.6, 110.4, 31.6 (t, J_{C-F}=22.0 Hz), 30.1; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.2, −114.1, −122.0, −122.3, −122.3, −123.1, −123.7, −126.5; HRMS (ESI) *m/z* calcd (M^++H) for $C_{17}H_9F_{17}NOS_2$ 629.9854, found 629.9871; Found: C 32.39%, H 1.27%, N 2.29%, S 10.31%; $C_{17}H_9F_{17}NOS_2$ requires C 32.44%, H 1.28%, N 2.23%, S 10.19%.

*3.6.19. Entry **19**: 2-benzothiazolyl 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluoro-1-decyl disulfide.* Yield 1.028 g, 59%, as a colourless solid; IR (CH_2Cl_2): ν_{max} 1245 (C–F), 469 (S–S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.92 (1H, dd, *J*=8.0, 1.2 Hz), 7.84 (1H, dd, *J*=8.0, 1.2 Hz), 7.47 (1H, td, *J*=8.0, 1.2 Hz), 7.38 (1H, td, *J*=8.0, 1.2 Hz), 3.20 (2H, m), 2.66 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 170.1, 154.9, 136.0, 126.5, 125.0, 122.5, 121.2, 31.7 (t, J_{C-F}=22.0 Hz), 30.0; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ_F: −81.2, −114.1, −122.0, −122.3, −122.3, −123.1, −123.6, −126.5; HRMS (ESI) *m/z* calcd (M^++H) for $C_{17}H_9F_{17}NS_3$ 645.9626, found 645.9609; Found: C 31.49%, H 1.19%, N 2.10%, S 14.80%; $C_{17}H_9F_{17}NS_3$ requires C 31.64%, H 1.25%, N 2.17%, S 14.90%.

*3.6.20. Entry **20**: 1-butyl 1-propyl disulfide[39].* Yield 0.308 g, 94%, as a clear-yellow oil; IR (CH_2Cl_2): ν_{max} 476 (S–S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 2.64 (4H, m), 1.65 (4H, m), 1.38 (2H, sext, *J*=7.4 Hz), 0.96 (3H, t, *J*=7.4 Hz), 0.89 (3H, t, *J*=7.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 41.2, 38.9, 31.3, 22.5, 21.6, 13.7, 13.1; HRMS (EI) *m/z* calcd (M^+) for $C_7H_{16}S_2$ 164.0693, found 164.0688.

*3.6.21. Entry **21**: tert-butyl 1-hexyl disulfide[40].* Yield 0.387 g, 94%, as a clear-yellow oil; IR (CH_2Cl_2): ν_{max} 476 (S–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.69 (2H, t, *J*=7.4 Hz), 1.63 (2H, quint, *J*=7.4 Hz), 1.31 (15H, m), 0.88 (3H, t, *J*=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 47.5, 41.0, 31.4, 29.9, 29.2, 28.2, 22.5, 14.0; HRMS (EI) *m/z* calcd (M^+) for $C_{10}H_{22}S_2$ 206.1163, found 206.1158.

*3.6.22. Entry **22**: 1-hexyl 2-hydroxyethyl disulfide.* Yield 0.295 g, 76%, as a clear-yellow oil; IR (CH_2Cl_2): ν_{max} 3351 (OH), 481 (S–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 3.88 (2H, t, *J*=5.9 Hz), 2.84 (2H, t, *J*=5.9 Hz), 2.70 (2H, t, *J*=7.5 Hz), 2.10 (1H, br s), 1.67 (2H, quint, *J*=7.5 Hz), 1.37 (2H, m), 1.29 (4H, m), 0.88 (3H, t, *J*=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 60.4, 41.2, 39.1, 31.3, 29.1, 28.1, 22.5, 13.9; HRMS (EI) *m/z* calcd (M^+) for $C_8H_{18}OS_2$ 194.0799, found 194.0794.

*3.6.23. Entries **23a**,**b**: 2-benzoxazolyl p-methoxyphenyl disulfide.* Yield for **23a**, 0.690 g, 88%; for **23b**, 0.674 g, 86%, as a yellow oil; IR (CH_2Cl_2): ν_{max} 500 (S–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.68 (3H, m), 7.49 (1H, m), 7.31 (2H, m), 6.86 (2H, d, *J*=9.0 Hz), 3.78 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 161.0, 161.0, 152.4, 141.9, 134.7, 132.0, 124.7, 124.6, 119.4, 114.9, 110.3, 55.3; HRMS (ESI) *m/z* calcd (M^++H) for $C_{14}H_{12}NO_2S_2$ 290.0309, found 290.0300.

*3.6.24. Entries **24a**,**b**: 2-benzothiazolyl p-methoxyphenyl disulfide[37].* Yield for **24a**, 0.751 g, 91%; for **24b**, 0.704 g, 85%, as a yellow semi-solid; IR (CH_2Cl_2): ν_{max} 500 (S–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.87 (1H, dd, *J*=7.8, 1.2 Hz), 7.80 (1H, dd, *J*=7.8, 1.2 Hz), 7.63 (2H, d, *J*=8.7 Hz), 7.43 (1H, td, *J*=7.8, 1.2 Hz), 7.33 (1H, td, *J*=7.8, 1.2 Hz), 6.86 (2H, d, *J*=8.7 Hz), 3.78 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 171.9, 160.8, 154.9, 135.8, 133.3, 132.6, 126.2, 124.6, 122.2, 121.1, 115.0, 55.4; HRMS (ESI) *m/z* calcd (M^++H) for $C_{14}H_{12}NOS_3$ 306.0081, found 306.0068.

*3.6.25. Entry **25**: 2-Hydroxyphenyl 2-methoxycarbonylphenyl disulfide.* Yield 0.679 g, 86%, as a yellow semi-solid; IR (CH_2Cl_2): ν_{max} 3424 (OH), 1710 (C=O), 490 (S–S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.26 (1H, dd, *J*=8.2, 1.0 Hz), 8.00 (1H, dd, *J*=7.6, 1.0 Hz), 7.60 (1H, m), 7.48 (1H, dd, *J*=7.6, 1.4 Hz), 7.28 (1H, m), 7.23 (1H, m), 6.95 (1H, dd, *J*=8.2, 1.4 Hz), 6.82 (1H, td, *J*=7.6, 1.2 Hz), 6.21 (1H, br s), 3.92 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 166.4, 156.2, 140.6, 133.5, 132.8, 131.4, 131.4, 127.9, 126.7, 125.9, 121.1, 120.8, 116.0, 52.4; HRMS (ESI) *m/z* calcd (M^++H) for $C_{14}H_{13}O_3S_2$ 293.0306, found 293.0309.

*3.6.26. Entry **26**: 2-Hydroxyphenyl p-methoxyphenyl disulfide.* Yield 0.600 g, 84%, as a yellow oil; IR (CH_2Cl_2): ν_{max} 3453 (OH), 498 (S–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.39 (2H, d, *J*=8.7), 7.27 (2H, m), 6.98 (1H, dd, *J*=8.6, 1.1 Hz), 6.84 (3H, m), 6.23 (1H, br s), 3.81 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 160.9, 156.6, 135.5, 135.1, 132.3, 127.2, 121.4, 120.7, 115.6, 114.8, 55.4; HRMS (ESI) *m/z* calcd (M^++H) for $C_{13}H_{13}O_2S_2$ 265.0357, found 265.0360.

*3.6.27. Entry **27**: 2-Hydroxyphenyl 2-pyridyl disulfide.* Yield 0.604 g, 95%, as a yellow solid; mp (ethanol) 92–95 °C; IR (CH_2Cl_2): ν_{max} 3474 (OH), 490 (S–S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 11.95 (1H, s), 8.62 (1H, m), 7.60 (2H, m), 7.33 (2H, m), 7.19 (1H, m), 7.02 (1H, dd, *J*=8.4, 1.2 Hz), 6.84 (1H, td, *J*=7.6, 1.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 160.0, 157.9, 148.9, 137.4, 137.1, 133.0, 122.0, 121.5, 120.3, 119.9, 117.8; HRMS (ESI) *m/z* calcd (M^++H) for $C_{11}H_{10}NOS_2$ 236.0204, found 236.0205; Found: C 56.12%, H 3.78%, N 5.70%, S 27.11%; $C_{11}H_9NOS_2$ requires C 56.15%, H 3.85%, N 5.95%, S 27.25%.

*3.6.28. Entries **28a**,**b**,**c**,**d**: p-methoxyphenyl p-tolyl disulfide[41].* Yield for **28a**, 0.418 g, 59%; for **28b**, 0.530 g, 75%; for **28c**, 0.411 g, 58%; for **28d**, 0.560 g, 79%, as a colourless solid; mp (ethanol) 44–46 °C (lit.[9] mp 46–47 °C); IR ν_{max} ($CHCl_3$) cm^{-1} 488 (S–S); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.42 (2H, d, *J*=8.9 Hz), 7.39 (2H, d, *J*=8.1 Hz), 7.12 (2H, d, *J*=8.1 Hz), 6.83 (2H, d, *J*=8.9 Hz), 3.79 (3H, s), 2.33 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 159.7, 137.5, 134.0, 131.9, 129.7, 129.1, 128.2, 114.6, 55.2, 21.0; HRMS (EI) *m/z* calcd (M^+) for $C_{14}H_{14}OS_2$ 262.0486, found 262.0471.

3.7. Synthesis of Boc or CBz protected L-cysteine

The title compounds were prepared by a modification of the known procedures by Myers[31a] and Threadgill.[31b] To a stirred suspension of L-cysteine ethyl ester hydrochloride (0.93 g, 5.00 mmol) in CH_2Cl_2 (40 mL) at −5 °C, was added solid $NaHCO_3$ (1.26 g, 15.00 mmol) and the slurry stirred for 10 min. To this suspension was added the protecting agent (di-*tert*-butyl dicarbonate (1.09 g, 5.00 mol) or benzyloxycarbonyl chloride (0.85 g, 5.00 mmol)) and the mixture allowed to stir for 12 h, slowly warming to room temperature. The reaction remained as a slurry throughout. The reaction was diluted with H_2O and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude material was purified by column chromatography with petroleum ether/ethyl acetate mixtures to obtain the desired compound.

3.7.1. N-tert-Butoxycarbonyl-L-cysteine ethyl ester[42]. Yield 1.22 g, 98%, as a colourless semi-solid; $[\alpha]_D^{20}$ +18.8 (c 1.0, $CHCl_3$), (lit.[43] $[\alpha]_D^{20}$ +20.0 (c 1.0, $CHCl_3$)); IR ν_{max} (CH_2Cl_2) cm^{-1} 3370 (NH), 2571 (SH), 1720 (C=O), 1393 and 1370 (O–C(CH_3)$_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 5.35 (1H, br s), 4.56 (1H, br s), 4.21 (2H, m), 3.16 (2H, br s), 1.46 (10H, s), 1.30 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 170.2, 155.1, 80.1, 61.8, 54.8, 28.3, 27.4, 14.2; HRMS (EI) *m/z* calcd (M^+) for $C_{10}H_{19}NO_4S$ 249.1035, found 249.1038.

3.7.2. N-Benzyloxycarbonyl-L-cysteine ethyl ester[44]. Yield 1.39 g, 98%, as a colourless semi-solid; $[\alpha]_D^{20}$ 18.2 (c 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) cm^{-1} 3348 (NH), 2572 (SH), 1723 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.37 (5H, m), 5.73 (1H, br s), 5.14 (2H, s), 4.65 (1H, br s), 4.25 (2H, m), 3.01 (2H, br s), 1.40 (1H, t, *J*=9.0 Hz), 1.30 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 169.8, 155.6, 136.1,

128.5, 128.2, 128.0, 67.1, 61.9, 55.2, 27.1, 14.1; HRMS (ESI) m/z calcd (M^++H) for $C_{13}H_{18}NO_4S$ 284.0957, found 284.0958.

3.7.3. N-Fmoc-S-trityl-L-cysteine methyl ester[45]. Prepared on a 1.00 mmol scale according to the procedure by Van der Klein[32a] and Nudelman[46] from *N*-Fmoc-*S*-trityl-L-cysteine-OH (0.586 g, 1.00 mmol) in CH_3COCl/MeOH (0.079 g, 1 mmol/5 mL) to give *N*-Fmoc-*S*-trityl-L-cysteine methyl ester (0.580 g, 97%) as a clear sticky substance; $[\alpha]_D^{20}$ +10.1 (c 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) cm^{-1} 3414 (NH), 1725 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.78 (2H, m), 7.63 (2H, br s), 7.42 (8H, m), 7.30 (8H, m), 7.23 (3H, m), 5.27 (1H, d, J=7.6 Hz), 4.40 (3H, m), 4.26 (1H, m), 3.74 (3H, s), 2.69 (2H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 174.7, 155.8, 144.2, 143.8, 141.3, 129.5, 128.1, 127.7, 127.1, 126.9, 125.1, 120.0, 67.2, 67.0, 52.8, 52.6, 47.1, 33.6; HRMS (ESI) m/z calcd (M^++H) for $C_{38}H_{34}NO_4S$ 600.2209, found 600.2210.

3.7.4. N-Fmoc-L-cysteine methyl ester[47]. Prepared on a 1.00 mmol scale according to the procedure by Moreau[33b] and Pearson[33a] from *N*-Fmoc-*S*-trityl-L-cysteine methyl ester (0.600 g, 1.00 mmol) using Et_3SiH/TFA (0.128 g, 1.10 mmol/0.40 mL) to give *N*-Fmoc-L-cysteine methyl ester (0.290 g, 81%) as a colourless semi-solid; $[\alpha]_D^{20}$ +17.3 (c 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) cm^{-1} 3316 (NH), 2575 (SH), 1737 (C=O), 1692 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.79 (2H, d, J=7.5 Hz), 7.62 (2H, d, J=7.5 Hz), 7.42 (2H, t, J=7.5 Hz), 7.34 (2H, t, J=7.5 Hz), 5.70 (1H, br s), 4.68 (1H, br s), 4.46 (2H, s), 4.25 (1H, t, J=6.8 Hz), 3.81 (3H, s), 3.01 (2H, s), 1.39 (1H, t, J=8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 170.4, 155.6, 143.6, 141.3, 127.8, 127.1, 125.0, 120.0, 67.1, 55.3, 52.8, 47.2, 27.1; HRMS (ESI) m/z calcd (M^++H) for $C_{19}H_{20}NO_4S$ 358.1113, found 358.1117.

3.8. Synthesis of unsymmetrical cysteine disulfides (29–31, Table 7)

*3.8.1. Entries **29a,b**: N-Boc, N-CBz-L-cysteine disulfide diethyl diester.* Yield for **29a**, 0.241 g, 91%; for **29b**, 0.235 g, 89%, as a clear sticky oil; $[\alpha]_D^{20}$ +39.4 (c 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) cm^{-1} 3354 (NH), 1715 (C=O), 464 (S–S); HPLC t_R=9.12 min (HPLC chromatogram can be found in the Supplementary data); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 (5H, m), 5.71 (1H, br s), 5.39 (1H, br s), 5.14 (2H, s), 4.65 (1H, br s), 4.58 (1H, br s), 4.22 (4H, m), 3.21 (2H, m), 3.15 (2H, m), 1.45 (9H, s), 1.29 (6H, t, J=7.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 170.5, 170.2, 155.6, 154.9, 136.1, 128.4, 128.1, 128.0, 80.1, 67.0, 61.9, 61.7, 53.4, 52.9, 41.3, 41.2, 28.2, 13.9, 13.9; HRMS (ESI) m/z calcd (M^++H) for $C_{23}H_{35}N_2O_8S_2$ 531.1835, found 531.1860.

*3.8.2. Entries **30a,b**: N-Boc, N-Fmoc-L-cysteine disulfide ethyl$_{(N\text{-}Boc)}$, methyl$_{(N\text{-}Fmoc)}$ diester.* Yield for **30a** on a 0.168 mmol scale of R^1SH, 0.091 g, 90%; for **30b** on a 0.239 mmol scale of R^1SH, 0.130 g, 90%, as a colourless semi-solid; $[\alpha]_D^{20}$ +45.5 (c 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) cm^{-1} 3426 (NH), 1715 (C=O), 462 (S–S); HPLC t_R=11.41 min (HPLC chromatogram can be found in the Supplementary data); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.78 (2H, d, J=7.6 Hz), 7.62 (2H, d, J=7.6 Hz), 7.41 (2H, t, J=7.3 Hz), 7.33 (2H, t, J=7.3 Hz), 5.77 (1H, br s), 5.40 (1H, br s), 4.69 (1H, br s), 4.59 (1H, br s), 4.43 (2H, d, J=6.8 Hz), 4.24 (3H, quint, J=7.0 Hz), 3.80 (3H, s), 3.20 (4H, m), 1.47 (9H, s), 1.30 (3H, t, J=7.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C: 170.8, 170.6, 155.6, 155.1, 143.7, 141.3, 127.7, 127.1, 125.1, 119.9, 80.2, 67.2, 61.9, 53.3, 53.0, 52.7, 47.1, 41.5, 41.0, 28.3, 14.1; HRMS (ESI) m/z calcd (M^+−t-Bu+2H) for $C_{24}H_{29}N_2O_6S_2$ 505.1467, found 505.1465.

*3.8.3. Entries **31a,b**: N-CBz, N-Fmoc-L-cysteine disulfide ethyl$_{(N\text{-}CBz)}$, methyl$_{(N\text{-}Fmoc)}$ diester.* Yield for **31a** on a 0.168 mmol scale of R^1SH, 0.098 g, 91%; for **31b** on a 0.413 mmol scale of R^1SH, 0.235 g, 89%, as a colourless semi-solid; $[\alpha]_D^{20}$ +37.0 (c 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) cm^{-1} 3425 (NH), 1713 (C=O), 462 (S–S); HPLC t_R=11.33 min (HPLC chromatogram can be found in the Supplementary data); ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.78 (2H, d, J=7.2 Hz), 7.62 (2H, d, J=7.2 Hz), 7.40 (2H, t, J=7.2 Hz), 7.34 (7H, m), 5.72 (2H, br s), 5.13 (2H, s), 4.68 (2H, m), 4.43 (2H, d, J=6.0 Hz), 4.24 (3H, m), 3.78 (3H, s), 3.20 (4H, m), 1.28 (3H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C: 170.8, 170.2, 155.7, 155.7, 143.7, 141.3, 136.1, 128.5, 128.2, 128.1, 127.7, 127.1, 125.1, 120.0, 67.2, 67.1, 62.1, 53.4, 53.3, 52.7, 47.1, 41.4, 41.1, 14.1; HRMS (ESI) m/z calcd (M^++H) for $C_{32}H_{35}N_2O_8S_2$ 639.1835, found 639.1827.

Acknowledgements

We thank the South African National Research Foundation, the University of Cape Town and the Claude-Leon Foundation for financial support.

Supplementary data

NMR spectra of all disulfides together with HPLC traces of the cysteine derivatves. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.02.077.

References and notes

1. Witt, D. *Synthesis* **2008**, 2491.
2. (a) Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 5677; (b) Arisawa, M.; Suwa, A.; Yamaguchi, M. *J. Organomet. Chem.* **2006**, *691*, 1159.
3. Zincke, T.; Frohneberg, W. *Berichte* **1909**, *42*, 2722.
4. Swan, J. M. *Nature* **1957**, *180*, 643.
5. (a) Hiskey, R. G.; Carroll, F. I.; Babb, R. M.; Bledsoe, J. O.; Puckett, R. T.; Roberts, B. W. *J. Org. Chem.* **1961**, *26*, 1152; (b) Hiskey, R. G.; Ward, B. F., Jr. *J. Org. Chem.* **1970**, *35*, 1118; (c) Alguindigue, S. L.; Lemma, K.; Ashby, M. T. *Heteroatom Chem.* **2007**, *18*, 467.
6. (a) Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* **1968**, *9*, 5907; (b) Mu, Y. Q.; Nodwell, M.; Pace, J. L.; Shaw, J. P.; Judice, J. K. *Biorg. Med. Chem. Lett.* **2004**, *14*, 735.
7. (a) Harpp, D. H.; Ash, D. K.; Back, T. G.; Gleason, J. G.; Orwig, B. A.; VanHorn, W. F.; Snyder, J. P. *Tetrahedron Lett.* **1970**, *11*, 3551; (b) Boustang, K. S.; Sullivan, A. B. *Tetrahedron Lett.* **1970**, *11*, 3547.
8. Thiosulfonates: Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S.; Davis, B. G. *J. Org. Chem.* **2005**, *70*, 9740.
9. Phosphorothioyldisulfides: Demkowicz, S.; Rachon, J.; Witt, D. *Synthesis* **2008**, 2033.
10. *S*-Alkylthioisothiouronium salts: Sirakawa, K.; Aki, O.; Tsujikawa, T.; Tsuda, T. *Chem. Pharm. Bull.* **1970**, *18*, 235.
11. Sulfenylthiocarbonates: Brois, S. J.; Pilot, J. F.; Barnum, H. W. *J. Am. Chem. Soc.* **1970**, *92*, 7629.
12. Alkylthiosulfonium salts: Chambert, S.; Gautier-Luneau, I.; Fontecave, M.; Décout, J.-L. *J. Org. Chem.* **2000**, *65*, 249.
13. 2-Pyridyl disulfides: Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C.; Pechet, M. M. *J. Org. Chem.* **1991**, *56*, 6697; For nitropyridyl variants, see: *Solid-Phase Synthesis*; Andreu, D.; Nicolas, E., Eds.; Kates, S. A., Albericio, F.; Marcel Dekker: New York, NY, 2000; p 365.
14. 2-Benzothiazolyl disulfides: Ternay, A. L.; Brzezinska, E. *J. Org. Chem.* **1994**, *59*, 8239.
15. *N*-Alkyltetrazolyl disulfides: Ohtani, M.; Narisada, N. *J. Org. Chem.* **1991**, *56*, 5475.
16. *N*-Trifluoroacetyl arenesulfenamides: Bao, M.; Shimizu, M.. *Tetrahedron* **2003**, *59*, 9655.
17. 4-Nitrosulfenanilides: Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron Lett.* **1986**, *27*, 1739.
18. Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411.
19. Hunter, R.; Caira, M.; Stellenboom, N. *J. Org. Chem.* **2006**, *71*, 8268.
20. Rees, C. W.; Storr, R. C. *J. Chem. Soc., Chem. Commun.* **1968**, 1305.
21. Abe, Y.; Nakabayashi, T.; Tsurugi, J. *Bull. Chem. Soc., Jpn.* **1973**, *46*, 1898.
22. Hunter, R.; Caira, M.; Stellenboom, N. *Ann. N.Y. Acad. Sci.* **2005**, *1056*, 234.
23. Brace, N. O. *J. Fluor. Chem.* **2000**, *105*, 11.
24. O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
25. Demkowicz, S.; Rachon, J.; Witt, D. *Synthesis* **2008**, *22*, 2033.
26. Hunter, R.; Stellenboom, N.; Caira, M. R. *Synlett* **2008**, 252.
27. Zuberi, S.; Glen, A.; Hider, R. C.; Bansal, S. S. *Tetrahedron Lett.* **1998**, *39*, 7567.
28. Fletcher, J. M.; Hughes, R. A. *Tetrahedron Lett.* **2004**, *45*, 6999.
29. Galande, A. K.; Spatola, A. F. *Org. Lett.* **2003**, *5*, 3431.
30. Vlahov, I. R.; Santhapuram, H. K. R.; Wang, Y.; Kleindl, F. Y.; Howard, S. J.; Westrick, E.; Reddy, J. A.; Leamon, C. P. *J. Org. Chem.* **2007**, *72*, 5968.
31. (a) Myers, A. G.; Gleason, J. L. *Org. Synth.* **1999**, *76*, 57; (b) Threadgill, M. D.; Gledhill, A. P. *J. Org. Chem.* **1989**, *54*, 2940.
32. (a) Van der Klein, P. A. M.; De Nooy, A. E. J.; Van der Marel, G. A.; Van Boom, J. H. *Synthesis* **1991**, *5*, 347; (b) Carolan, J. V.; Butler, S. J.; Joliffe, K. A. *J. Org. Chem.* **2009**, *74*, 2992.
33. (a) Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739; (b) Moreau, X.; Campagne, J.-M. *J. Org. Chem.* **2003**, *68*, 9874.
34. Kice, J. L.; Morkved, E. H. *J. Am. Chem. Soc.* **1963**, *85*, 3472.

35. Stellenboom, N.; Hunter, R.; Caira, M. R.; Bourne, S. A.; Cele, K.; Qwebani, T.; le Roex, T. *ARKIVOC* **2007**, *9*, 53.
36. Walter, W.; Hell, P. M. *Liebigs Ann. Chem.* **1969**, *727*, 35.
37. Brzezinska, E.; Ternay, A. L., Jr. *J. Org. Chem.* **1994**, *59*, 8239.
38. Peters, E. C.; Brittain, S. M.; Brock, A.; Ficarro, S.; Salomon, A. *PCT Int. Appl.* **2005**, WO 2005050226.
39. Gupta, D.; Knight, A. R.; Smith, P. J. *Can. J. Chem.* **1981**, *59*, 543.
40. Kuliev, A. M.; Kuliev, A. B.; Zeinalova, G. A.; Gasanov, M. S.; Damirova, F. G. *Neftekhimiya* **1977**, *17*, 464.
41. Caputo, R.; Ferreri, C.; Palumbo, G. *Tetrahedron* **1986**, *42*, 5377.
42. Namyslo, J. C.; Stanitzek, C. *Synthesis* **2006**, *20*, 3367.
43. Song, L.-C.; Ge, J.-H.; Yan, J.; Wang, H.-T.; Luo, X.; Hu, Q.-M. *Eur. J. Inorg. Chem.* **2008**, 164.
44. Olsen, R. K.; Kini, G. D.; Hennen, W. J. *J. Org. Chem.* **1985**, *50*, 4332.
45. Osawa, T.; Ato, S.; Akiha, M.; Kakimoto, N. *Jpn. Kokai Tokkyo Koho* **1999**, JP 11269178.
46. Nudelman, A.; Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun.* **1998**, *28*, 471.
47. Kelleman, A.; Mattern, R.-H.; Pierschbacher, M. D.; Goodman, M. *Biopolymers* **2003**, *71*, 686.