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ARTICLE

On the synthesis of α-amino sulfoxides†

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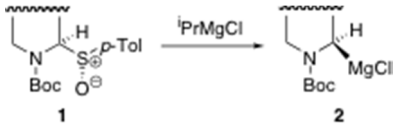
A synthetic study on the preparation of *N*-Boc α-amino sulfoxides has revealed an unexpected instability which is believed to be due to α-elimination of the sulfoxide to give an iminium ion. Full synthetic details are reported on two main synthetic routes: lithation and sulfinate trapping of *N*-Boc heterocycles and oxidation of *N*-Boc α-amino sulfides. Six novel α-amino sulfoxides were successfully prepared and isolated. It is speculated that four other α-amino sulfoxides were synthesised but could not be isolated due to their propensity to α-eliminate the sulfoxide. Ultimately, a stable, cyclic *N*-Boc α-amino sulfoxide was prepared and this successful synthesis relied on the α-amino sulfoxide being part of a bicyclic [3.1.0] fused ring system that could not undergo α-elimination of the sulfoxide.

Introduction

Our group has an ongoing interest in the development of methodology for the asymmetric synthesis of saturated nitrogen heterocycles (*e.g.* pyrrolidines[1] and piperidines[2]), efforts which have been spurred on by the prevalence of such heterocyclic motifs in active pharmaceutical ingredients.[3] The most streamlined approach to α-substituted heterocycles is direct α-functionalisation[4] and, in this context, Beak's lithiation-trapping of *N*-Boc activated heterocycles[5,6] using *s*-BuLi and diamines (such as TMEDA or (–)-sparteine) is one of the most reliable and predictable methods.[7] However, a key limitation of the asymmetric variant is that reactions rarely generate products with ≥95:5 er. To address this limitation, we have been exploring the synthesis and applications of *N*-Boc α-amino-substituted sulfoxides **1**. In particular, it was our intention that *N*-Boc α-amino sulfoxides **1** of 99:1 dr and 99:1 er would be direct precursors to chiral Grignard reagents **2** of 99:1 er *via* sulfoxide to magnesium exchange (Scheme 1). This strategy was successfully demonstrated with the synthesis of a bicyclic α-substituted *N*-Boc heterocycle.[8] However, in developing the methodology, we were unable to synthesise a number of *N*-Boc α-amino sulfoxides **1** which we believed was due to their unexpected instability. Our efforts on the synthesis of *N*-protected α-amino sulfoxides **1** are the subject of this paper.



Scheme 1

Before commencing the synthesis of α-amino sulfoxides **1**, a literature survey was carried out on all three classes of sulfur-containing α-amino compounds with a focus on pyrrolidines and piperidines (Figure 1). There were numerous examples of α-amino sulfides of which *N*-acyl pyrrolidine **3**,[9] *N*-Boc piperidine **4**[5] and *N*-Boc pyrrolidine **5**[10] are representative. Sulfide **3** was prepared *via* an intramolecular Pummerer reaction, sulfide **4** was synthesised by Beak-style α-lithiation-trapping of the parent *N*-Boc piperidine and sulfide **5** was accessed *via* iminium ion chemistry.

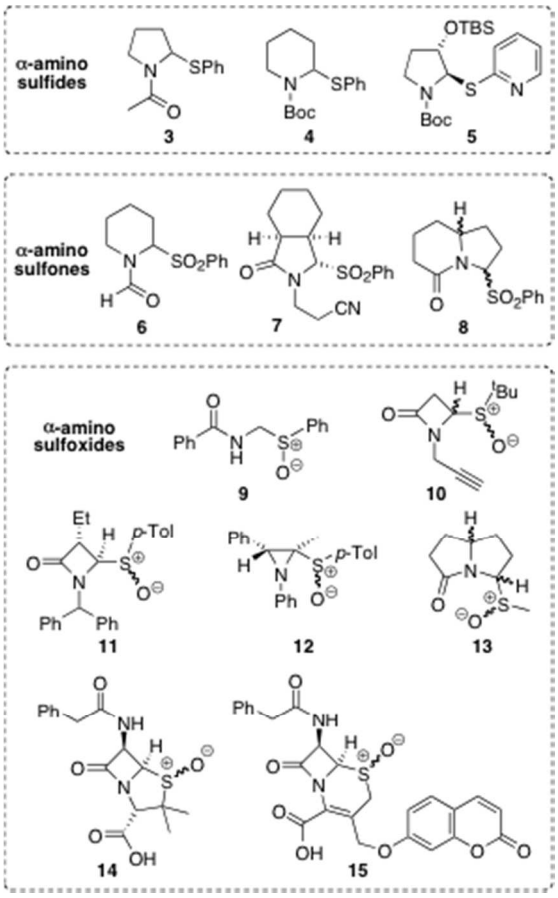


Figure 1

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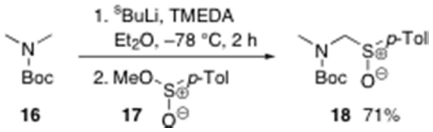
In contrast, there were limited examples of pyrrolidinyl and piperidinyl α-amino sulfones and sulfoxides and Figure 1 represents a comprehensive list of the classes of known compounds. There were a few α-amino sulfones such as **6**[11] and **7**[12] (prepared by reaction of the iminium ion with benzenesulfinic acid) and **8**[13] (synthesised by *m*-CPBA oxidation of the sulfide and proceeding *via* the α-amino sulfoxide). It is useful to note in passing that α-amino sulfones **6** and **7** have been used as precursors to iminium ions (*via* α-elimination) although Lewis acid activation is typically required.[11,12] To the best of our knowledge, there is only one known acyclic α-amino sulfoxide, **9**,[14] prepared by oxidation of the corresponding sulfide. Interestingly, α-elimination of the sulfoxide in **9** was relatively facile to give the putative iminium ion (which could be trapped with methanol). Examples of cyclic α-amino sulfoxides include azetidinones **10**[15] and **11**,[16] both synthesised by sulfide oxidation and aziridines such as **12**[17] which was prepared by cyclisation of the amine onto an α-chloro sulfoxide. The only pyrrolidine-containing α-amino sulfoxide that we are aware of is **13**[18] which was obtained by oxidation of the sulfide. Examples of penicillin-like[19] and cephalosporin-like[20] sulfoxides such as **14** and **15** respectively have also been described; both were synthesised by sulfur oxidation.

In this paper, we present an overview of all our synthetic efforts towards preparing α-amino sulfoxides **1**. In general, the approaches adopted to prepare α-amino sulfides, sulfones and sulfoxides **3**-**15** were investigated. Surprisingly, our synthetic efforts revealed an apparent instability of α-amino sulfoxides **1** and we conclude with some general guidelines about the types of compounds that have been successfully synthesised.

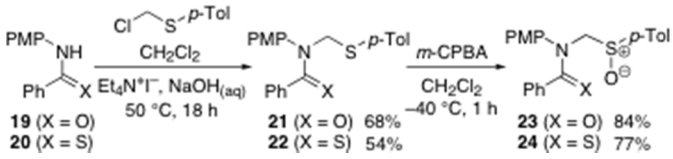
Results and discussion

To start with, direct α-lithiation-sulfinate trapping from a *N*-Boc activated amine was explored. Thus, lithiation of *N*-Boc dimethylamine **16** was accomplished using *s*-BuLi/TMEDA in Et_2O at –78 °C. Pleasingly, subsequent reaction with known[21] methyl *p*-toluenesulfinate **17** gave a 71% yield of α-amino sulfoxide **18** (Scheme 2). Such a good yield of **18** was possible only if 1% Et_3N was added to the eluent during the column chromatography. Without Et_3N, significant decomposition occurred, potentially *via* α-elimination of the sulfoxide to give the iminium ion.



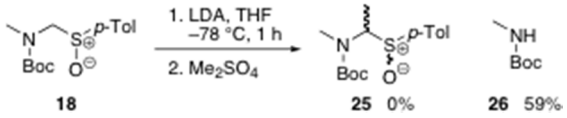
Scheme 2

The analogous acyclic *N*-protected α-amino sulfoxides **23** and **24** were synthesised *via* a different approach as outlined in Scheme 3. Alkylation of amide **19**[22] using chloromethyl *p*-tolylsulfide[23] under phase-transfer conditions[24] gave α-amino sulfide **21** (68% yield). Thioamide **22** was prepared from **20** in a similar fashion. *m*-CPBA oxidation proceeded uneventfully to give good yields of **23** and **24**. *N*-Protected α-amino sulfoxides **23** and **24** appeared to be more stable then α-amino sulfoxide **18**: no decomposition was noted upon column chromatography even in the absence of Et_3N. This may be due to extra delocalisation of the nitrogen lone pair disfavouring α-elimination of the sulfoxide to the iminium ion.



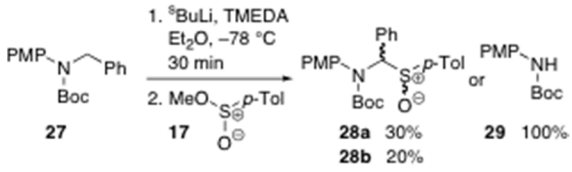
Scheme 3

With the successful synthesis of α-amino sulfoxides **18**, **23** and **24**, our attention switched to compounds containing further substitution α to the sulfoxide. The attempted synthesis of α-amino sulfoxide **25** is shown in Scheme 4. Deprotonation of α-amino sulfoxide **18** with LDA was followed by reaction with dimethylsulfate. After purification by chromatography (with 1% Et_3N in the eluent), the only isolable product was *N*-Boc methylamine **26** (59% yield). Since **26** was not evident in the ^1H NMR spectrum of the crude product, we speculate that adduct **25** could have formed but then converted into **26** *via* an iminium ion and hydrolysis during the chromatography. *N*-Boc methylamine **26** could not have been formed from unreacted **18** since **18** is stable to chromatography in the presence of Et_3N.



Scheme 4

Our approach to α-amino sulfoxides **28a/b** involved starting with the substituent in place and then lithiating and trapping with methyl *p*-toluenesulfinate **17**. Lithiation-trapping of *N*-Boc benzylamine **27** is well-established from the work of Beak and co-workers.[25] Thus, lithiation of **27** using *s*-BuLi/TMEDA and trapping with methyl *p*-toluenesulfinate **17** gave, after chromatography (with Et_3N), separable diastereomers **28a** (30% yield) and **28b** (20% yield) of undetermined stereochemistry (Scheme 5). α-Amino sulfoxides **28a/b**, which were fully characterised, were on the borderline of stability on silica (even in the presence of Et_3N). Frustratingly, we were unsuccessful in reproducing the isolation of **28a/b**: all subsequent attempts led, after chromatography, to the generation of quantitative yields of *N*-Boc amine **29** (presumably formed *via* α-elimination of the sulfoxide and hydrolysis of the so-generated iminium ion) even though **28a/b** were evident in the ^1H NMR spectra of the crude product.



Scheme 5

Next, we moved on to investigating the preparation of cyclic α-amino sulfoxides **31** and **35** derived from *N*-Boc pyrrolidine **30** and *N*-Boc piperidine **33** respectively. α-Amino sulfoxides **31** and **35** were key targets as they could ultimately provide ready access to chiral α-amino Grignard reagents **2** suitable for incorporation into potential pharmaceutical building blocks. To start with, *N*-Boc pyrrolidine **30** was subjected to diamine-free

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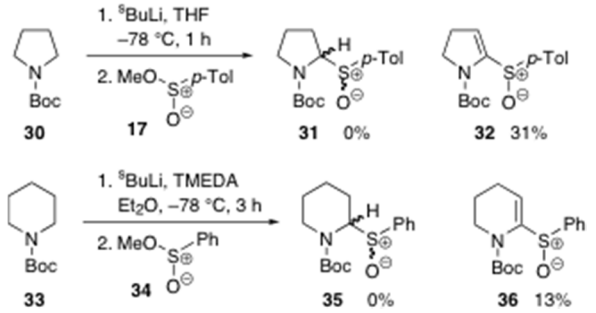
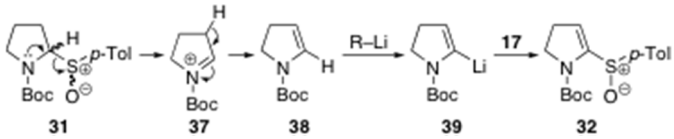
lithiation (*s*-BuLi, THF, –78 °C, 1 h).[26] Disappointingly, reaction of the organolithium with methyl *p*-toluenesulfinate **17** did not lead to the formation of any of the desired α-amino sulfoxide **31**. After chromatography, the only product we could isolate pure and in substantial amounts was vinyl sulfoxide **32**, which was fully characterised (Scheme 6). Use of different lithiation conditions (*e.g. s*-BuLi/(–)-sparteine, Et_2O, –78 °C) or reverse addition of the organolithium to the electrophile gave similar results. A similar, but lower-yielding outcome was observed with *N*-Boc piperidine **33** (lithiation using *s*-BuLi/TMEDA, Et_2O, –78 °C[5] and trapping with methyl benzenesulfinate **34**): vinyl sulfoxide **36** was isolated in 13% yield (Scheme 6).



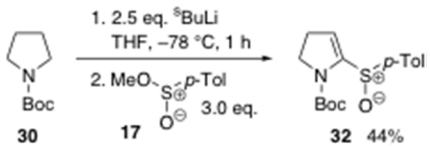
Scheme 6

Our suggested explanation to account for the formation of vinyl sulfoxide **32** (and analogously, **36**) is presented in Scheme 7. We believe that formation of the desired α-amino sulfoxide **31** may well be occurring by lithiation-trapping. However, as noted in other substituted α-amino sulfoxides (*e.g.* **25** and **28a**/**b**), α-elimination of the sulfoxide could occur to give iminium ion **37** which can rearrange to enecarbamate **38**. Vinylic lithiation of enecarbamates like **38** is well-known and facile.[27] In this case, untrapped lithiated *N*-Boc pyrrolidine or excess *s*-BuLi could lithiate **38** to give vinylic organolithium **39** which is ultimately trapped by methyl *p*-toluenesulfinate **17** to give vinyl sulfoxide **32**. We also considered the direct conversion of **31** into **38** *via* sulfoxide cycloreversion but this seemed less likely at such low reaction temperatures (–78 °C).[28]



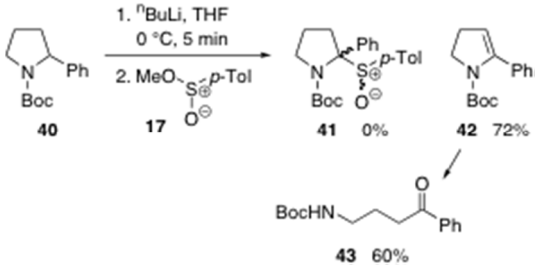
Scheme 7

The proposed mechanism for the formation of vinyl sulfoxide **32** would require 2 equivalents of base to give a quantitative yield. Therefore, we attempted to optimise the preparation of vinyl sulfoxide **32**, imagining that it could be a useful synthetic intermediate. Treatment of *N*-Boc pyrrolidine **30** with 2.5 equivalents of *s*-BuLi in THF and trapping with 3.0 equivalents of methyl *p*-toluenesulfinate **17** gave a 44% yield of vinyl sulfoxide **32** (Scheme 8).



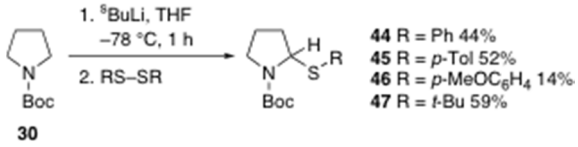
Scheme 8

The synthesis of α-amino sulfoxide **41** from an alternative *N*-Boc pyrrolidine, phenyl-substituted pyrrolidine **40**,[2a,29] was also explored. Lithiation of **40** was accomplished using *n*-BuLi in THF at 0 °C for 5 min according to the known procedure.[2a] Subsequent reaction with methyl *p*-toluenesulfinate **17** did not give any of the hoped-for product **41**. Instead, enecarbamate **42** was isolated in 72% yield after chromatography (Scheme 9). In this case, vinylic lithiation-trapping could not occur as enecarbamate **42** is already substituted. Nevertheless, this represents a convenient way of synthesising enecarbamates such as **42** from the corresponding saturated heterocycle (**40**). As noted previously by Tomooka, enecarbamate **42** readily rearranged to *N*-Boc keto-amine **43** on standing (Scheme 9).[30]



Scheme 9

At this stage, we were disappointed not to be able to prepare a wide range of α-amino sulfoxides and the evidence suggested that some compounds were unstable due to α-elimination of the sulfoxide group. With this issue in mind, we set about trying to prepare cyclic *N*-protected α-amino sulfoxides where the propensity for α-elimination might be reduced. Our first approach was to modify the sulfoxide group itself, with the idea that more electron-rich sulfoxides might disfavour α-elimination and so could be stable enough to be isolated. To this end, the synthesis and oxidation of *N*-Boc α-amino sulfides was investigated. Lithiation of *N*-Boc pyrrolidine **30** and disulfide trapping[5] proceeded smoothly to give stable α-amino sulfides **44**-**47** in 14-59% yields (Scheme 10).



Scheme 10

The results of the attempted oxidation of α-amino sulfides **44**-**47** are shown in Table 1. Unfortunately, no α-amino sulfoxides were isolated. Starting from α-amino sulfide **44**, oxidation with *m*-CPBA at room temperature gave a 31% yield of known[31] hydroxy pyrrolidine **48** (entry 1). Presumably, oxidation to the sulfoxide occurred but was followed by α-elimination to the iminium ion which was intercepted by water during work-up. To be certain that over-oxidation to the sulfone was not the source of the problem, a protocol developed by Ramesh *et al.*[32] (*m*-CPBA, KF, MeCN-water, rt) was employed. However, hydroxy pyrrolidine **48** was the only product in 57% yield (entry 2). Lower temperature *m*-CPBA oxidation (–40 °C)[33] on all four α-amino sulfides **44**-**47** including more electron-rich sulfides (*p*-$MeOC_6H_4$– and *t*-Bu– substituents) was uniformly unsuccessful: hydroxy pyrrolidine **48** was generated in 74-86%

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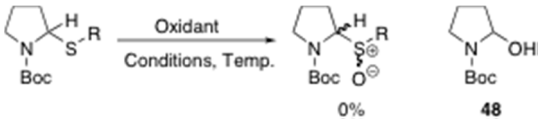
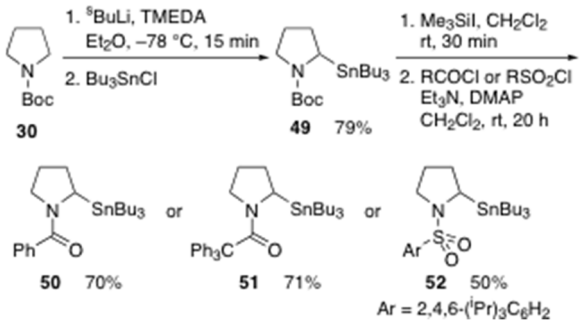
yields (entries 3-6). Finally, using α-amino sulfide **45**, two other oxidation conditions were explored: use of hydrogen peroxide in hexafluoroisopropanol[34] and trimethylsilyl chloride/potassium superoxide[35] each gave hydroxypyrrolidine **48** as the sole product (entries 7 and 8). The failure to prepare pyrrolidinyl α-amino sulfoxides from α-amino sulfides **44**-**47** was particularly disappointing as this is the route that has been used most often to prepare the stable α-amino sulfoxides **9**-**15** (Figure 1). It seems that minor structural differences and/or different *N*-protecting groups (*e.g.* amides) are apparently responsible for whether α-amino sulfoxides are stable and isolable or not.

Table 1. Oxidation of *N*-Boc α-amino sulfides.



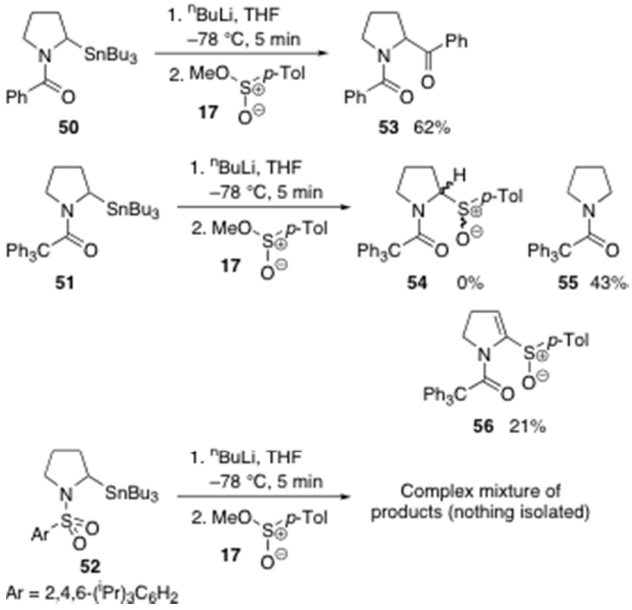
Entry	Sulfide	Oxidant	Conditions	Temp/°C	% Yield of **48**
1	**44**	*m*-CPBA	Na_2CO_3, CH_2Cl_2	rt	31
2	**44**	*m*-CPBA	KF, MeCN-H_2O	rt	57
3	**44**	*m*-CPBA	CH_2Cl_2	–40	86
4	**45**	*m*-CPBA	CH_2Cl_2	–40	81
5	**46**	*m*-CPBA	CH_2Cl_2	–40	74
6	**47**	*m*-CPBA	CH_2Cl_2	–40	77
7	**45**	H_2O_2	HFIP	rt	43
8	**45**	Me_3SiCl/KO_2	MeCN	–15	52

Since six of the seven known classes of α-amino sulfoxides **9**-**15** (Figure 1) have the nitrogen as part of an amide, we next targeted amide-protected pyrrolidinyl α-amino sulfoxides **50** and **51**; a sulfonamide (**52**) was also included as part of this study. Our plan was to use tin-lithium exchange to access the organolithium intermediate. Thus, lithiation-trapping of *N*-Boc pyrrolidine **30** using *s*-BuLi/TMEDA gave known[6] stannane **49**. Boc deprotection of **49** was best realised using Me_3SiI as described by Gawley[36] and subsequent acylation/sulfonylation then delivered **50**-**52** in 50-71% yields (Scheme 11).



Scheme 11

Starting with *N*-benzamide stannane **50**, treatment with *n*-BuLi in THF at –78 °C over 5 min led to tin-lithium exchange but subsequent attempted trapping with methyl *p*-toluenesulfinate **17** gave no α-amino sulfoxide. Instead, the only product isolated was keto-amide **53** in 62% yield (Scheme 12). Keto-amide **53** was also formed when we tried to trap the lithiated *N*-benzoyl pyrrolidine with methanol which indicated that use of the sulfinate **17** was not the problem. Presumably, the lithiated *N*-benzoyl pyrrolidine forms and then attacks the amide carbonyl group on starting stannane **50**. Subsequent tin-lithium exchange and protonation would then give keto-amide **53**. Due to this nucleophilic attack on the amide, a more sterically hindered amide was investigated, namely trityl amide **51**. Tin-lithium exchange and trapping with methyl *p*-toluenesulfinate **17** gave amide **55** (43% yield) resulting from protonation of the lithiated *N*-tritylamide and vinyl sulfoxide **56** (21% yield) (Scheme 12). The hoped-for α-amino sulfoxide **54** may well have formed but its subsequent reaction led to vinyl sulfoxide **56**, as observed with *N*-Boc pyrrolidine **30** (Scheme 6). With *N*-sulfonyl stannane **52**, equipped with an *ortho*-lithiation-resistant[37] 2,4,6-tri-*i*-Pr-benzenesulfonyl group, tin-lithium exchange and attempted trapping with methanol or methyl *p*-toluenesulfinate **17** led only to a complex mixture of unidentified products (Scheme 12). In fact, tin-lithium exchange on *N*-sulfonyl stannanes like **52** has not, to the best of our knowledge, been reported previously.



Scheme 12

At this point, we concluded that for cyclic *N*-acyl or *N*-Boc α-amino sulfoxides, it was probably necessary to build in specific structural aspects that would disfavour α-elimination. Using azetidinones **10**, **11**, **14** and **15** (Figure 1) as a guide, the synthesis of α-amino sulfoxide **58** was investigated. The thioamide functionality was chosen as Hodgson has reported a convenient procedure for the lithiation-trapping of *N*-thioamide azetidine **57**.[38] Lithiation of thioamide **57** was achieved with *s*-BuLi/TMEDA in THF at –78 °C and subsequent trapping with methyl *p*-toluenesulfinate **17** gave a 91:9 mixture of diastereomeric α-amino sulfoxides **58**. After chromatography, only the major diastereomer (unknown stereochemistry) was isolated in 9% yield (Scheme 13). Despite this reproducibly low yield, this was our first example of a stable, isolable cyclic α-amino sulfoxide. It appears that α-elimination is disfavoured as the iminium ion would be part of a 4-membered ring.

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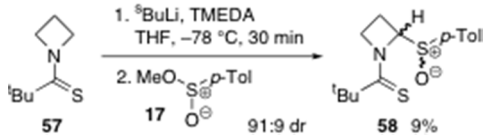
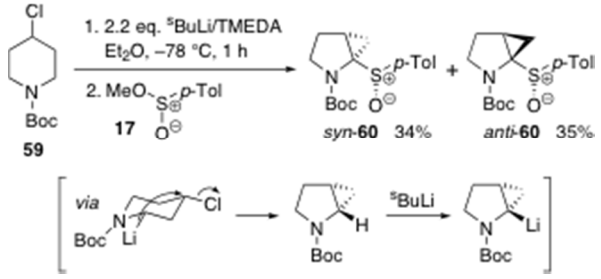


Scheme 13

Building on this preliminary success, an alternative strategy for disfavouring α-elimination was ultimately devised. By building the α-amino sulfoxide functionality into a [3.1.0] fused bicycle as exemplified by *syn*-/*anti*-**60**, α-elimination should be prohibited and did indeed lead to stable α-amino sulfoxides. The α-substituted [3.1.0] bicyclic framework can be crafted from 4-chloro *N*-Boc piperidine **59** as reported by Beak[25a,39] (and proceeding *via* α-lithiation, cyclisation, a second α-lithiation of the now more acidic cyclopropyl proton and trapping, Scheme 14). Thus, lithiation of 4-chloro *N*-Boc piperidine **59** using 2.2 equivalents of *s*-BuLi/TMEDA in Et_2O at –78 °C presumably led to the lithiated bicyclic *N*-Boc pyrrolidine. Subsequent trapping with methyl *p*-toluenesulfinate **17** gave separable and stable α-amino sulfoxides *syn*-**60** (34% yield) and *anti*-**60** (35%) (Scheme 14), whose stereochemical assignment has been described elsewhere.[8] Our successful application of *syn*-**60** of 99:1 er as a precursor to an enantiomerically pure Grignard reagent has previously been reported.[8]



Scheme 14

Conclusions

In summary, our efforts on the synthesis of a range of structurally diverse α-amino sulfoxides have been presented. To our surprise, some targets were inaccessible and we attribute this not to an inability to synthesise them but to their propensity to α-eliminate the sulfoxide moiety to give an iminium ion. Despite this issue, which appears to be more of a problem with α-amino sulfoxides than with α-amino sulfides or sulfones, several novel α-amino sulfoxides (**18**, **23**, **24**, **28a/b**, **58** and *syn*-/*anti*-**60**) have been successfully isolated as part of our study. We believe that several of the α-amino sulfoxides were synthesised but not isolated (**25**, **31**, **35**, **41** and **54**). A full spectrum of stability for the new α-amino sulfoxides and the previously reported α-amino sulfoxides **9**-**15** is presented in Figure 2. In our opinion, the key aspect affecting the stability is α-elimination of the sulfoxide. If α-elimination can be disfavoured by incorporating the nitrogen into `an amide and/or a 3- or 4-membered ring then stable α-amino sulfoxides (**9**-**15**, **23**, **24**, **58** and *syn*-/*anti*-**60**) result. Further work is required to establish unequivocally that sulfoxide α-elimination is the reason for our inability to synthesise particular α-amino sulfoxides.

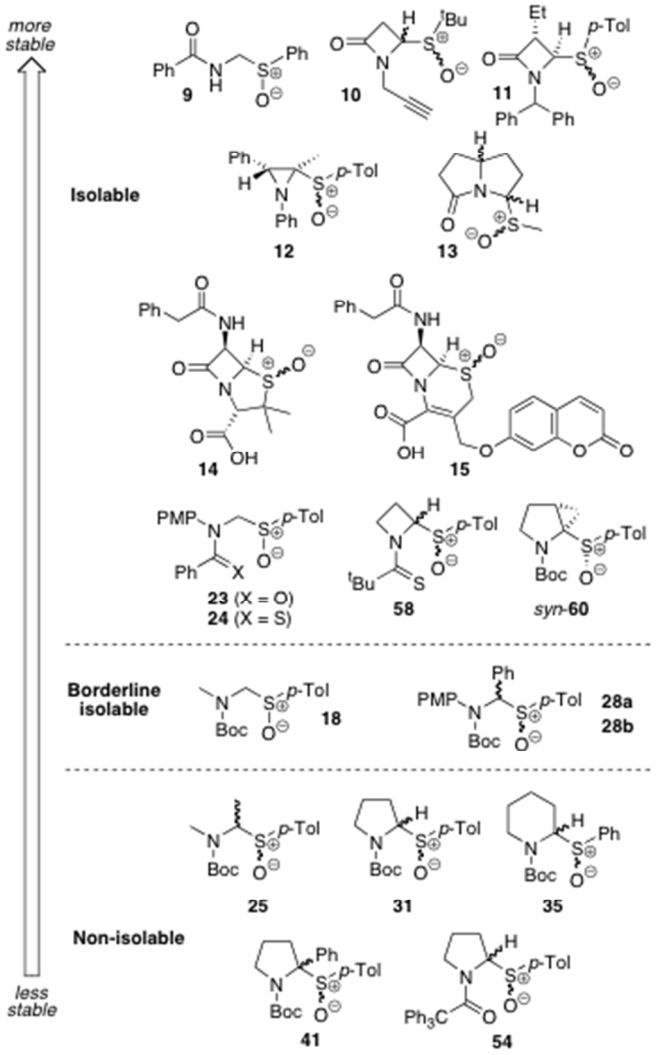


Figure 2

Experimental

General

All non-aqueous reactions were carried out under O_2-free Ar using flame-dried glassware. All reagents were used as purchased without further purification unless otherwise stated. Alkyllithiums were titrated against *N*-benzylbenzamide before use. All diamines and electrophiles were distilled over CaH_2 before use. Et_2O and THF were freshly distilled from sodium and benzophenone ketyl. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. Water is distilled water. Brine refers to a saturated aqueous solution of NaCl.

The following compounds were synthesised according to the reported procedures: *N*-Boc dimethylamine **16**,[31] methyl *p*-toluenesulfinate **17**,[8] *N*-(4-methoxyphenyl)benzamide **19**,[22] *N*-Boc, *N*-benzyl *p*-anisidine **27**,[25b] *N*-Boc pyrrolidine **30**,[31] *N*-Boc piperidine **33**,[27] *N*-Boc 2-phenyl pyrrolidine **40**,[29] *N*-thiopivaloyl azetidine **57**[38] and *N*-Boc 4-chloro piperidine **59**.[8]

Procedures and Characterisation Data

***N*-Methyl *N*-*p*-tolylsulfinylmethyl carbamic acid *tert*-butyl ester 18.** *s*-BuLi (1.00 mL of a 1.3 M solution in hexanes, 1.30

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mmol, 1.3 eq.), was added dropwise to a stirred solution of *N*-Boc dimethylamine **16** (145 mg, 1.00 mmol, 1.0 eq.) and TMEDA (151 mg, 0.19 mL, 1.30 mmol, 1.3 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 2 h. Then, methyl *p*-toluenesulfinate **17** (340 mg, 2.00 mmol, 2.0 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone with 1% Et_3N as eluent gave sulfoxide **18** (202 mg, 71%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone with 1% Et_3N) 0.3; IR (Film) 2977, 2930, 1712 (C=O), 1493, 1454, 1370, 1288, 1163, 1045, 871 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 7.55 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.51 (d, J = 8.0 Hz, 1H, *m*-C_6H_4Me), 7.35 (d, J = 8.0 Hz, 1H, *o*-C_6H_4Me), 7.33 (d, J = 8.0 Hz, 1H, *o*-C_6H_4Me), 4.58 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 4.37 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 4.30 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 4.11 (d, J = 13.0 Hz, 0.5H, NCH_AH_B), 3.06 (s, 1.5H, NMe), 2.94 (s, 1.5H, NMe), 2.42 (s, 1.5H, C_6H_4Me), 2.41 (s, 1.5H, C_6H_4Me), 1.43 (s, 4.5H, CMe_3), 1.39 (s, 4.5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.2 (C=O), 154.2 (C=O), 142.0 (*ipso*-$C_6H_4S(O)$), 141.7 (*ipso*-$C_6H_4S(O)$), 138.7 (*ipso*-C_6H_4Me), 138.4 (*ipso*-C_6H_4Me), 130.1 (Ar), 129.9 (Ar), 124.3 (Ar), 124.2 (Ar), 81.2 (CMe_3), 81.0 (CMe_3), 74.6 (NCH_2), 74.5 (NCH_2), 37.0 (NMe), 36.3 (NMe), 28.2 (CMe_3), 28.0 (CMe_3), 21.4 (br, C_6H_4Me); MS (ESI) *m/z* 306 [$(M + Na)^+$, 100]; HRMS *m/z* calcd for $C_{14}H_{21}NO_3S$ $(M + Na)^+$ 306.1134, found 306.1135 (−0.3 ppm error).

Chloromethyl *p*-tolylsulfide.[23] *N*-Chlorosuccinimide (3.67 g, 27.5 mmol, 1.1 eq., recrystallised from glacial AcOH) was added to a stirred solution of methyl *p*-tolylsulfide (3.45 g, 25.0 mmol, 1.0 eq.) in $CHCl_3$ (25 mL) at 0 °C. The resulting solution was allowed to warm to rt over 5 min and then stirred at rt for 18 h. Then, 4% $NaI_{(aq)}$ (50 mL) was added and the two layers were separated. The organic layer was washed with 10% $Na_2S_2O_{3(aq)}$ (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a 90:10 mixture (by ^1H NMR spectroscopy) of chloromethyl *p*-tolylsulfide and methyl *p*-tolylsulfide (4.12 g, 90% yield of chloromethyl *p*-tolylsulfide) as a pale yellow oil, ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 2 H, *o*-C_6H_4Me), 7.18 (d, J = 8.0 Hz, 2 H, *m*-C_6H_4Me), 4.92 (s, 2H, CH_2), 2.36 (s, 3H, Me). Attempted purification by flash column chromatography on silica gel or by fractional distillation led to product decomposition. Therefore, the crude product was used in the next step without further purification.

***N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfanylmethyl benzamide 21.** A 90:10 mixture (by ^1H NMR spectroscopy) of chloromethyl *p*-tolylsulfide and methyl *p*-tolylsulfide (1.80 g, 9.38 mmol of chloromethyl *p*-tolylsulfide, 2.5 eq.) was added to a stirred solution of tetraethylammonium iodide (430 mg, 1.88 mmol, 0.5 eq.) and benzamide **19** (850 mg, 3.75 mmol, 1.0 eq.) in CH_2Cl_2 (7.5 mL) at rt. The resulting solution was cooled to 0 °C and 50% $NaOH_{(aq)}$ (17.5 mL) was added. The resulting solution was stirred and heated at 50 °C for 18 h. Then, the solution was allowed to cool to rt and poured into saturated $NH_4Cl_{(aq)}$ (50 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 65:35 petrol-EtOAc as eluent gave benzamide **21** (922 mg, 67%) as a colourless oil, R_F (65:35 petrol-EtOAc) 0.4; IR (film) 2955, 1649 (C=O), 1510, 1493, 1446, 1372, 1250, 1144, 1039, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 5H, Ar), 7.16 (t, J = 7.5 Hz, 2H, Ar), 7.04 (d, J = 8.0 Hz, 2H, Ar), 6.93 (d, J = 8.0 Hz, 2H, Ar), 6.69 (d, J = 8.0 Hz, 2H, Ar), 5.30 (s, 2H, NCH_2), 3.73 (s, 3H, OMe), 3.00 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O), 158.3 (*ipso*-C_6H_4OMe), 137.1 (*ipso*-Ar), 135.3 (*ipso*-Ar), 135.1 (*ipso*-Ar), 132.2 (Ar), 130.9 (*ipso*-Ar), 130.4 (Ar), 129.7 (Ar), 129.4 (Ar), 128.6 (Ar), 127.6 (Ar), 114.2 (Ar), 55.9 (NCH_2), 55.3 (OMe), 21.0 (Me); MS (ESI) *m/z* 386 [$(M + Na)^+$, 100], 364 [$(M + H)^+$, 20], 240 (50); HRMS *m/z* calcd for $C_{22}H_{21}NO_2S$ $(M + Na)^+$ 386.1185, found 386.1175 (+2.6 ppm error).

***N*-(4-Methoxyphenyl)thiobenzamide 20.** Phosphorous(V) sulfide (918 mg, 4.13 mmol, 1.25 eq.) was added to a stirred solution of benzamide **19** (750 mg, 3.30 mmol, 1.0 eq.) in pyridine (15 mL) at rt under Ar. The resulting solution was stirred and heated at 75 °C for 6 h. The solution was allowed to cool to rt and then poured into 1 M $HCl_{(aq)}$ (50 mL). 1 M $HCl_{(aq)}$ was added until pH 3 was obtained. The resulting solution was stirred for 2 h and then extracted with CH_2Cl_2 (3 × 50 mL). Combined organic extracts were washed with 1 M $HCl_{(aq)}$ (50 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-EtOAc as eluent gave thiobenzamide **20** (320 mg, 40%) as a pale yellow oil, R_F (4:1 petrol-EtOAc) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 8.94 (br s, 1H, NH), 7.88 (dd, J = 7.0, 1.5 Hz, 2H, *o*-Ph), 7.67 (d, J = 8.5 Hz, 2H, Ar), 7.52 (tt, J = 7.0, 1.5 Hz, 1H, *p*-Ph), 7.45 (td, J = 7.0 1.5 Hz, 2H, *m*-Ph), 6.98 (d, J = 8.5 Hz, 2H, Ar), 3.86 (s, 3H, OMe); MS (ESI) *m/z* 266 [$(M + Na)^+$, 20], 244 [$(M + H)^+$, 100], 159 (30), 141 (30), 125 (30); HRMS *m/z* calcd for $C_{14}H_{13}NOS$ $(M + H)^+$ 244.0791, found 244.0786 (+2.0 ppm error).

***N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfanylmethyl thiobenzamide 22.** A 90:10 mixture (by ^1H NMR spectroscopy) of chloromethyl *p*-tolylsulfide and methyl *p*-tolylsulfide (481 mg, 2.48 mmol of chloromethyl *p*-tolylsulfide, 2.5 eq.) was added to a stirred solution of tetraethylammonium iodide (112 mg, 0.50 mmol, 0.5 eq.) and thiobenzamide **20** (240 mg, 0.99 mmol, 1.0 eq.) in CH_2Cl_2 (4.5 mL) at rt. The resulting solution was cooled to 0 °C and then 50% $NaOH_{(aq)}$ (2.5 mL) was added. The resulting solution was stirred and heated at 50 °C for 18 h. Then, the solution was allowed to cool to rt and poured into saturated $NH_4Cl_{(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-EtOAc as eluent gave sulfanyl thiobenzamide **22** (204 mg, 54%) as a colourless oil, R_F (9:1 petrol-EtOAc) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H, Ar), 7.24-7.14 (m, 5H, Ar), 6.93 (br s, 2H, Ar), 6.70 (d, J = 8.5 Hz, 2H, Ar), 6.60 (d, J = 8.5 Hz, 2H, Ar), 4.64 (s, 2H, NCH_2), 3.74 (s, 3H, OMe), 2.35 (s, 3H, Me); MS (ESI) *m/z* 402 [$(M + Na)^+$, 100], 380 [$(M + H)^+$, 50]; HRMS *m/z* calcd for $C_{22}H_{21}NOS_2$ $(M + Na)^+$ 402.0962, found 402.0968 (+2.5 ppm error).

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***N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfinylmethyl benzamide 23.** *m*-CPBA (68 mg of ~77% purity, 0.31 mmol, 1.1 eq.) was added to a stirred solution of sulfanyl benzamide **21** (100 mg, 0.28 mmol, 1.0 eq.) in CH_2Cl_2 (1.8 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 EtOAc-petrol as eluent gave sulfoxide **23** (88 mg, 84%) as an orange oil, R_F (7:3 EtOAc-petrol) 0.3; IR (film) 3056, 2932, 2837, 1650 (C=O), 1513, 1446, 1359, 1294, 1178, 1084, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.32 (d, J = 7.5, 2H Hz, *o*-Ph), 7.30 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 7.26 (br t, J = 7.5 Hz, 1H, *p*-Ph), 7.16 (t, J = 7.5 Hz, 2H, *m*-Ph), 7.10 (d, J = 8.5 Hz, 2H, Ar), 6.69 (d, J = 8.5 Hz, 2H, Ar), 5.20 (d, J = 12.5 Hz, 1H, NCH_AH_B), 4.49 (d, J = 12.5 Hz, 1H, NCH_AH_B), 3.70 (s, 3H, OMe), 2.38 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 158.3 (*ipso*-C_6H_4OMe), 141.7 (*ipso*-Ar), 138.8 (*ipso*-Ar), 135.9 (*ipso*-Ar), 134.3 (*ipso*-Ar), 130.2 (Ar), 129.9 (Ar), 128.9 (Ar), 128.8 (Ar), 127.8 (Ar), 124.3 (Ar), 114.3 (Ar), 76.9 (NCH_2), 55.3 (OMe), 21.4 (Me); MS (ESI) *m/z* 402 [$(M + Na)^+$, 100], 240 [$(M - S(O)C_6H_4Me)^+$, 50]; HRMS *m/z* calcd for $C_{22}H_{21}NO_3S$ $(M + Na)^+$ 402.1134, found 402.1124 (+2.5 ppm error).

***N*-(4-Methoxyphenyl)-*N*-*p*-tolylsulfinylmethyl thiobenzamide 24.** *m*-CPBA (141 mg of ~70% purity, 0.57 mmol, 1.1 eq.) was added to a stirred solution of sulfanyl thiobenzamide **22** (200 mg, 0.52 mmol, 1.0 eq.) in CH_2Cl_2 (3.5 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 EtOAc-petrol as eluent gave sulfoxide **24** (158 mg, 77%) as a viscous orange foam, R_F (7:3 EtOAc-petrol) 0.2; IR ($CHCl_3$) 2833, 1613 (C=S), 1502, 1443, 1242, 1178, 1047, 956, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.34-7.19 (m, 7H, Ar), 6.69 (d, J = 8.0 Hz, 2H, Ar), 6.51 (d, J = 8.5 Hz, 2H, Ar), 4.57 (d, J = 13.0 Hz, 1H, NCH_AH_B), 4.45 (d, J = 13.0 Hz, 1H, NCH_AH_B), 3.74 (s, 3H, OMe), 2.40 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 208.1 (C=S), 156.1 (*ipso*-C_6H_4OMe), 141.7 (*ipso*-Ar), 140.1 (*ipso*-Ar), 135.1 (br, *ipso*-Ar), 130.0 (*ipso*-Ar), 129.6 (Ar), 128.5 (Ar), 128.0 (Ar), 127.5 (Ar), 124.7 (Ar), 122.7 (Ar), 113.9 (Ar), 60.4 (NCH_2), 55.8 (OMe), 55.3 (OMe), 21.4 (Me), 14.6 (Me); MS (ESI) *m/z* 396 [$(M + H)^+$, 100]; HRMS *m/z* calcd for $C_{22}H_{21}NO_2S_2$ $(M + H)^+$ 396.1086, found 396.1092 (−0.4 ppm error).

***N*-(*tert*-Butoxycarbonyl)methylamine 26.** *n*-BuLi (100 µL of a 2.5 M solution in hexanes, 0.26 mmol, 1.3 eq.) was added dropwise to a stirred solution of diisopropylamine (26 mg, 36 µL, 0.26 mmol, 1.3 eq.) in THF (1 mL) at −78 °C under Ar. The resulting solution was warmed to 0 °C and stirred for 15 min and then cooled to −78 °C. Then, a solution of sulfoxide **18** (67 mg, 0.22 mmol, 1.0 eq.) in THF (2 mL) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C for 1 h. Then, Me_2SO_4 (42 mg, 31 µL, 0.49 mmol, 1.5 eq.) was added and the mixture was allowed to warm to rt over 2 h. Then, saturated $NH_4Cl_{(aq)}$ (4 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 96:4 CH_2Cl_2-acetone with 1% Et_3N as eluent gave *N*-Boc methylamine **26** (17 mg, 59%) as a colourless oil, R_F (96:4 CH_2Cl_2-acetone with 1% Et_3N) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (br s, 1H, NH), 2.83 (br s, 3H, NMe), 1.46 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 156.2 (C=O), 155.9 (C=O), 80.1 (CMe_3), 79.8 (CMe_3), 32.7 (Me), 32.5 (Me), 28.3 (CMe_3). Spectroscopic data consistent with those reported in the literature.[40]

***tert*-Butyl 4-methoxyphenyl(phenyl(p-tolylsulfinyl)methyl) carbamate 28a and 28b.** *s*-BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc *N*-benzyl *p*-anisidine **27** (313 mg, 1.0 mmol, 1.0 eq.) and TMEDA (151 mg, 194 µL, 1.3 mmol, 1.3 eq.) in Et_2O (2 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, methyl *p*-tolylsulfinate **17** (255 mg, 1.5 mmol, 1.5 eq.) was added. The resulting solution was stirred at −30 °C for 10 min and then allowed to warm to rt over 1 h. Then, MeOH (1 mL), saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone with 0.5% Et_3N as eluent gave sulfoxide **28a** (135 mg, 30%) as a yellow solid, mp 65-68 °C, R_F (98:2 CH_2Cl_2-acetone with 0.5% Et_3N) 0.2; IR ($CHCl_3$) 2963, 1691 (C=O), 1494, 1347, 1224, 1142, 1018, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H, Ar), 7.33-7.22 (m, 7H, Ar), 6.68 (d, J =9.0 Hz, 2H, Ar), 6.56 (br d, J = 8.0 Hz, 2H, Ar), 5.57 (s, 1H, NCH), 3.77 (s, 3H, OMe), 2.43 (s, 3H, Me), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 158.3 (C=O), 155.6 (*ipso*-Ar), 153.1 (*ipso*-Ar), 142.1 (*ipso*-Ar), 140.9 (*ipso*-Ar), 140.7 (*ipso*-Ar), 137.9 (*ipso*-Ar), 136.4 (*ipso*-Ar), 135.4 (Ar), 134.4 (Ar), 131.0 (Ar), 130.1 (Ar), 129.7 (Ar), 129.6 (Ar), 129.0 (Ar), 128.0 (Ar), 127.8 (Ar), 126.8 (Ar), 124.3 (Ar), 114.1 (Ar), 113.3 (Ar), 80.1 (CMe_3), 55.5 (OMe or NCH), 55.2 (OMe or NCH), 28.3 (CMe_3), 28.1 (CMe_3), 21.3 (Me), 21.2 (Me); MS (ESI) *m/z* 474 [$(M + Na)^+$, 2], 452 [$(M + H)^+$, 1], 393 (20), 352 (50), 312 (100), 256 (20); HRMS (ESI) *m/z* calcd for $C_{26}H_{29}NO_4S$ $(M + H)^+$ 452.1890, found 452.1919 (+5.5 ppm error) and sulfoxide **28b** (92 mg, 20%) as a yellow solid, mp 68-70 °C, R_F (98:2 CH_2Cl_2-acetone with 0.5% Et_3N) 0.1; IR ($CHCl_3$) 2964, 1691 (C=O), 1494, 1224, 1143, 1042, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.17 (m, 3H, Ar), 7.17-7.03 (m, 6H, Ar), 6.88-6.76 (m, 4H, Ar), 6.33-5.93 (m, 1H, NCH), 3.84 (s, 3H, OMe), 2.31 (s, 3H, Me), 1.74-1.27 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 158.3 (C=O), 155.6 (*ipso*-Ar), 153.1 (*ipso*-Ar), 142.1 (*ipso*-Ar), 141.0 (*ipso*-Ar), 140.8 (*ipso*-Ar), 137.9 (*ipso*-Ar), 136.4 (*ipso*-Ar), 135.4 (Ar), 134.4 (Ar), 131.4 (Ar), 131.0 (Ar), 130.1 (Ar), 129.7 (Ar), 129.6 (Ar), 129.0 (Ar), 128.0 (Ar), 127.8 (Ar), 126.8 (Ar), 124.3 (Ar), 114.1 (Ar), 113.3 (Ar), 80.1 (CMe_3), 55.5 (OMe or NCH), 55.2 (OMe or NCH), 28.3 (CMe_3), 28.1 (CMe_3), 21.5 (Me), 21.2 (Me); MS (ESI) *m/z* 474 [$(M + Na)^+$, 10], 452 [$(M + H)^+$, 5], 393 (40), 352 (60), 312 (100), 256 (20); HRMS (ESI) *m/z* calcd for $C_{26}H_{29}NO_4S$ $(M + H)^+$ 452.1890, found 452.1902 (+4.1 ppm error).

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Subsequent attempts to repeat this lithiation-trapping reaction were unsuccessful and sulfoxides **28a** and **28b** were not isolated probably due to their instability on silica.

***N*-*tert*-Butoxycarbonyl-5-(*p*-tolylsulfinyl)-2,3-dihydropyrrole 32.** *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **30** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, methyl *p*-toluenesulfinate **17** (510 mg, 3.0 mmol, 2.0 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave dihydropyrrole **32** (145 mg, 31%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2980, 1678 (C=O), 1369, 1306, 1153, 1093, 901, 809, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (br d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.24 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 5.96 (t, J = 3.0 Hz 1H, =CH), 3.97 (br s, 1H, NCH), 3.85-3.76 (m, 1H, NCH), 2.84-2.74 (m, 1H, CH), 2.64 (dddd, J = 17.0, 11.5, 6.0, 3.0 Hz, 1H, CH), 2.37 (s, 3H, Me), 1.37 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 174.3 (C=O), 150.2 (C=O), 142.1 (i*pso*-Ar), 140.9 (=C), 140.8 (=C), 136.5 (Ar), 135.4 (Ar), 130.2 (Ar), 129.6 (Ar), 127.7 (Ar), 126.6 (*ipso*-Ar), 126.2 (*ipso*-Ar), 124.3 (=CH), 82.7 (*C*Me_3), 46.4 (NCH_2), 32.9 (CH_2), 28.1 (C*Me*$_3$), 28.0 (C*Me*$_3$), 21.5 (br, Me), 17.4 (CH_2); (MS (ESI) *m/z* 330 [$(M + Na)^+$, 100], 208 (40), 238 (100); HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NO_3S$ $(M + Na)^+$ 330.1134, found, 330.1122 (+3.7 ppm error).

s-BuLi (1.92 mL of a 1.3 M solution in hexanes, 2.50 mmol, 2.5 eq.) was added to a stirred solution of *N*-Boc pyrrolidine **30** (171 mg, 1.00 mmol, 1.0 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, methyl *p*-toluenesulfinate **17** (510 mg, 3.0 mmol, 3.0 eq.) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave dihydropyrrole **32** (136 mg, 44%) as a colourless oil.

***N*-*tert*-Butylcarbonyl-6-(phenylsulfinyl)-3,4-dihydro-2*H*-pyridine 36.** *s*-BuLi (2.50 mL of a 1.3 M solution in hexanes, 3.25 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc piperidine **33** (463 mg, 2.50 mmol, 1.0 eq.) and TMEDA (378 mg, 0.49 mL, 3.25 mmol, 1.3 eq.) in Et_2O (8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, methyl benzenesulfinate **34** (624 mg, 4.00 mmol, 1.6 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc as eluent gave tetrahydropyridine **36** (100 mg, 13%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.30; IR (Film) 2975, 1693 (C=O), 1511, 1454, 1391, 1366, 1246, 1166, 1033, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H, *o*-Ph), 7.41-7.40 (m, 3H, Ph), 6.37 (t, J = 3.5 Hz, 1H, =CH), 3.97 (br d, J = 11.5 Hz, 1H, NCH), 2.71 (br s, 1H, NCH), 2.39 (ddt, J = 18.5, 6.5, 3.5 Hz, 1H, CH), 2.28 (dddd, J = 18.5, 10.0, 7.0, 3.5 Hz, 1H, CH), 1.86-1.69 (m, 2H, CH), 1.37 (s, 9H, CMe_3); ^{13}C NMR (rotamers) (100.6 MHz, $CDCl_3$) δ 152.3 (C=O), 144.7 (*ipso*-Ph), 143.5 (=C) 131.0 (Ph), 128.9 (Ph), 128.7 (Ph), 126.4 (Ph), 126.1 (Ph), 113.7 (br, =CH), 82.1 (br, *C*Me_3), 44.9 (NCH_2), 28.1 (C*Me*$_3$), 23.2 (CH_2), 22.0 (CH_2); MS (ESI) *m/z* 330 [$(M + Na)^+$, 100], 308 [$(M + H)^+$, 30], 252 (70); HRMS *m/z* calcd for $C_{16}H_{21}NO_3S$ $(M + Na)^+$ 330.1134, found 330.1127 (+2.2 ppm error).

***tert*-Butyl 5-phenyl-2,3-dihydro-1H-pyrrole-1-carboxylate 42 and *tert*-butyl 4-oxo-4-phenylbutylcarbamate 43.** *n*-BuLi (520 µL of a 2.5 M solution in hexanes, 1.3 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc 2-phenylpyrrolidine **40** (247 mg, 1.0 mmol, 1.0 eq.) in THF (10 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 5 min. Then, methyl *p*-tolylsulfinate **17** (340 mg, 2.0 mmol, 2.0 eq.) was added. The reaction was stirred at 0 °C for 10 min and then allowed to warm to rt over 30 min. Then, MeOH (0.6 mL), saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 petrol-Et_2O with 0.5% Et_3N as eluent gave dihydropyrrole **42** (178 mg, 72%) as a yellow oil, R_F (9:1 petrol-Et_2O) 0.2; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H, Ph), 5.23 (t, J = 3.0 Hz, 1H, C=CH), 4.05 (t, J = 9.0 Hz, 2H, NCH_2), 2.62 (td, J = 9.0, 3.0 Hz, 2H, CH_2), 1.19 (s, 9H, CMe_3). On standing, this compound was unstable and converted into *N*-Boc aminophenone **43** (158 mg, 60%) as an off-white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.5 Hz, 2H, *o*-Ph), 7.55 (t, J = 7.5 Hz, 1H, *p*-Ph), 7.45 (t, J = 7.5 Hz, 2H, *m*-Ph), 4.75 (br s, 1H, NH), 3.22 (q, J = 7.0 Hz, 2H, NCH_2), 3.02 (t, J = 7.0 Hz, 2H, CH_2CO), 1.93 (quin, J = 7.0 Hz, 2H, CH_2), 1.41 (s, 9H, CMe_3). Spectroscopic data of **43** consistent with those reported in the literature.[30]

***N*-*tert*-Butylcarbonyl-2-(phenylsulfanyl)pyrrolidine 44.** *s*-BuLi (2.62 mL of a 1.3 M solution in hexanes, 3.40 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **30** (445 mg, 2.60 mmol, 1.0 eq.) in THF (10 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, a solution of diphenyl disulfide (1.14 g, 5.2 mmol, 2.0 eq.) in THF (2 mL) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave sulfide **44** (301 mg, 44%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.7; IR (film) 2976, 2931, 1695 (C=O), 1444, 1406, 1367, 1143, 1078, 1049, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.55-7.42 (m, 2H, Ph), 7.31-7.29 (m, 3H, Ph), 5.39 (br s, 0.4H, NCH), 5.29-5.28 (m, 0.6H, NCH), 3.51-3.34 (m, 1.2H, NCH), 3.33-3.22 (m, 0.8H, NCH), 2.20-1.98 (m, 2.4H, CH), 1.93-1.83 (m, 1.6H, CH), 1.45 (s, 3.6H, CMe_3), 1.35 (s, 5.4H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.4 (C=O), 134.4 (*ipso*-Ph), 134.1 (*ipso*-Ph), 133.9 (Ph),

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128.9 (Ph), 128.7 (Ph), 127.8 (Ph), 127.6 (Ph), 127.3 (Ph), 82.6 (*C*Me$_3$), 79.8 (*C*Me$_3$), 66.9 (NCH), 66.6 (NCH), 46.1 (NCH$_2$), 45.4 (NCH$_2$), 33.8 (CH$_2$), 33.1 (CH$_2$), 28.3 (C*Me$_3$*), 28.0 (C*Me$_3$*), 22.8 (CH$_2$), 22.1 (CH$_2$); MS (ESI) *m/z* 302 [(M + Na)$^+$, 100], 208 (25), 114 (50); HRMS *m/z* calcd for $C_{15}H_{21}NO_2S$ (M + Na)$^+$ 302.1185, found, 302.1181 (+1.4 ppm error).

***N-tert*-Butylcarbonyl-2-(*p*-tolylsulfanyl)pyrrolidine 45.** *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **30** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, a solution of *p*-tolyl disulfide (739 mg, 3.0 mmol, 2.0 eq.) in THF (2 mL) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave sulfide **45** (319 mg, 52%) as a colourless oil, R_F (98:2 CH_2Cl_2-acetone) 0.40; IR (film) 2974, 2933, 1710 (C=O), 1527, 1390, 1366, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.43 (d, J = 7.5 Hz, 0.8H, *o*-C_6H_4Me), 7.38 (d, J = 7.5 Hz, 1.2H, *o*-C_6H_4Me), 7.12 (d, J = 7.5 Hz, 2H, *m*-C_6H_4Me), 5.32 (br s, 0.4H, NCH), 5.22 (br d, J = 5.5 Hz, 0.6H, NCH), 3.46-3.39 (m, 1.2H, NCH), 3.30-3.27 (m, 0.8H, NCH), 2.34 (s, 3H, Me), 2.21-2.03 (m, 2.4H, CH), 2.01-1.86 (m, 1.6H, CH), 1.45 (s, 3.6H, CMe$_3$), 1.36 (s, 5.4H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.7 (C=O), 138.3 (*ipso*-Ar), 135.1 (Ar), 130.3 (*ipso*-Ar), 129.8 (Ar), 80.1 (*C*Me$_3$), 67.1 (NCH), 45.6 (NCH$_2$), 33.8 (CH$_2$), 32.5 (CH$_2$), 28.5 (C*Me$_3$*), 21.3 (Me); MS (ESI) *m/z* 316 [(M + Na)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{23}NO_2S$ (M + Na)$^+$ 316.1342, found 316.1342 (0.0 ppm error).

***N-tert*-Butylcarbonyl-2-(*p*-methoxyphenylsulfanyl)pyrrolidine 46.** *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **30** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, *p*-methoxyphenyldisulfide (745 mg, 3.0 mmol, 2.0 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-Et_2O as eluent gave sulfide **46** (65 mg, 14%) as a colourless oil, R_F (98:2 CH_2Cl_2-Et_2O) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 7.48 (d, J = 8.0 Hz, 0.8H, *o*-C_6H_4OMe), 7.42 (d, J = 8.0 Hz, 1.2H, *o*-C_6H_4OMe), 6.84 (d, J = 8.0 Hz, 2H, *m*-C_6H_4OMe), 5.25 (br s, 0.4H, NCH), 5.16 (br d, J = 6.0 Hz, 0.6H, NCH), 3.80 (s, 3H, C_6H_4O*Me*), 3.45-3.28 (m, 2H, NCH), 2.14-1.99 (m, 2.4H, CH), 1.89-1.81 (m, 1.6H, CH), 1.43 (s, 3.6H, CMe$_3$), 1.36 (s, 5.4H, CMe$_3$); MS (ESI) *m/z* 332 [(M + Na)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{23}NO_3S$ (M + Na)$^+$ 332.1291, found 332.1289 (+0.5 ppm error).

***N-tert*-Butylcarbonyl-2-(*tert*-butylsulfanyl)pyrrolidine 47.** *s*-BuLi (1.50 mL of a 1.3 M solution in hexanes, 1.95 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **30** (257 mg, 1.50 mmol, 1.0 eq.) in THF (6 mL) at −78 °C under Ar. Then, *tert*-butyldisulfide (535 mg, 3.0 mmol, 2.0 eq) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 petrol-Et_2O as eluent gave sulfide **47** (230 mg, 59%) as a colourless oil, R_F (4:1 petrol-Et_2O) 0.40; IR (film) 2979, 1689 (C=O), 1393, 1367, 1254, 1163, 1117, 1042, 921, 870 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (50:50 mixture of rotamers) δ 5.22 (br s, 0.5H, NCH), 5.03 (br s, 0.5H, NCH), 3.39-3.34 (m, 1H, NCH), 3.30-3.22 (m, 1H, NCH), 2.20-2.03 (m, 2H, CH), 1.99-1.85 (m, 2H, CH), 1.44 (br s, 9H, CMe$_3$), 1.38 (br s, 9H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 153.4 (C=O), 82.7 (*C*Me$_3$), 79.4 (*C*Me$_3$), 60.7 (NCH), 45.0 (br, NCH$_2$), 43.1 (br, NCH$_2$), 36.7 (CH$_2$), 35.6 (CH$_2$), 31.5 (C*Me$_3$*), 28.5 (C*Me$_3$*); MS (ESI) *m/z* 282 [(M + Na)$^+$, 90], 210 (50), 114 (100); HRMS *m/z* calcd for $C_{13}H_{25}NO_2S$ (M + Na)$^+$ 282.1498, found 282.1477 (+7.7 ppm error).

***N-tert*-Butyl carbonyl-2-hydroxypyrrolidine 48.** *m*CPBA (77 mg of ~77% purity, 0.35 mmol, 1.0 eq) was added to a stirred solution of phenylsulfanyl pyrrolidine **44** (100 mg, 0.35 mmol, 1.0 eq.) and Na_2CO_3 (80 mg, 0.74 mmol, 2.1 eq.) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and CH_2Cl_2 (7 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-aceteone as eluent gave recovered sulfanyl pyrrolidine **44** (26 mg, 26%) as a colourless oil and hydroxy pyrrolidine **48** (21 mg, 31%) as a colourless oil, R_F (9:1 CH_2Cl_2-acetone) 0.3; IR (Film) 3452 (OH), 2976, 1695 (C=O), 1478, 1392, 1254, 1163, 1112, 1041, 916 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 5.48 (br s, 0.6H, NCH), 5.39 (br m, 0.4H, NCH), 3.56-3.46 (m, 1H, NCH), 3.34-3.17 (m, 1H, NCH), 2.11-1.78 (m, 4H, CH), 1.50 (s, 3.6H, CMe$_3$), 1.47 (s, 5.4H, CMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.1 (C=O), 81.8 (NCHOH), 80.0 (*C*Me$_3$), 45.9 (NCH$_2$), 32.6 (CH$_2$), 28.4 (C*Me$_3$*), 22.7 (CH$_2$); MS (ESI) *m/z* 379 [(M Dimer + Na)$^+$, 100], 266 (50), 210 [(M + Na)$^+$, 20]; HRMS *m/z* calcd for $C_9H_{17}NO_3$ (M + Na)$^+$ 210.1101, found 210.101 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[31]

*m*CPBA (89 mg of ~77% purity, 0.41 mmol, 1.1 eq) was added to a stirred solution of KF (40 mg, 0.69 mmol, 1.8 eq.) in 4:1 MeCN-water (3 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. Then, phenylsulfanyl pyrrolidine **44** (107 mg, 0.38 mmol, 1.0 eq.) was added. The resulting solution was stirred at 0 °C for 30 min. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and Et_2O (7 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 7 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **48** (40 mg, 57%) as a colourless oil.

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*m*CPBA (208 mg of ~77% purity, 1.20 mmol, 1.1 eq.) was added to a stirred solution of phenylsulfanyl pyrrolidine **44** (309 mg, 1.10 mmol, 1.0 eq.) in CH_2Cl_2 (2.2 mL) at −40 °C under Ar. The resulting solution was stirred at −40 °C for 1 h. Then, saturated $Na_2SO_{3(aq)}$ (7 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **48** (179 mg, 86%) as a colourless oil.

The above procedure was repeated using *p*-tolylsulfanyl pyrrolidine **45** (81%), *p*-methoxyphenylsulfanyl pyrrolidine **46** (74%), *t*-butylsulfanyl pyrrolidine **47** (77%).

H_2O_2 (0.07 mL of a 30% aqueous solution, 0.61 mmol, 1.8 eq.) was added dropwise to a stirred solution of sulfanyl pyrrolidine **45** (100 mg, 0.34 mmol, 1.0 eq.) in hexafluoroisopropanol (0.7 mL) at rt under Ar. The resulting solution was stirred at rt for 10 min. Then, saturated $Na_2SO_{3(aq)}$ (5 mL) and Et_2O (5 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-aceteone as eluent gave recovered sulfanyl pyrrolidine **45** (42 mg, 42%) and hydroxy pyrrolidine **48** (26 mg, 43%) as a colourless oil.

A solution of Me_3SiCl (47 μL, 0.37, 1.1 eq.) in MeCN (1 mL) was added dropwise to a stirred solution of KO_2 (52 mg, 0.73, 2.15 eq.) and sulfanyl pyrrolidine **45 (**100 mg, 0.34 mmol, 1.0 eq.) in MeCN (3 mL) at −15 °C under Ar. The resulting solution was stirred at −15 °C for 5 h. Then, 1M $HCl_{(aq)}$ (5 mL) was added and the solution was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 CH_2Cl_2-acetone as eluent gave hydroxy pyrrolidine **48** (31 mg, 52%) as a colourless oil.

2-(Tributylstannyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 49: *s*-BuLi (10.0 mL of a 1.3 M solution in hexanes, 13.0 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **30** (1.71 g, 10.0 mmol, 1.0 eq.) and TMEDA (1.51 g, 1.94 mL, 13.0 mmol, 1.3 eq.) in Et_2O (56 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 15 min. Then, Bu_3SnCl (4.0 mL, 15.0 mmol, 1.5 eq.) was added. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to rt over 16 h. Then, saturated $NH_4Cl_{(aq)}$ (40 mL) and Et_2O (100 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 petrol-EtOAc as eluent gave stannyl pyrrolidine **49** (3.64 g, 79%) as a colourless oil, R_F (98:2 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 3.69 (dd, J = 8.5, 2.0 Hz, 0.25H, NCH), 3.45-3.23 (m, 2H, NCH), 3.22-3.12 (m, 0.75H, NCH), 2.27-2.03 (m, 1H, CH), 1.97-1.75 (m, 2H, CH), 1.56-1.40 (m, 6H, CH), 1.48 (s, 2.25H, CMe_3), 1.43 (s, 6.75H, CMe_3), 1.35-1.23 (m, 6H, CH), 0.95-0.81 (m, 15H, CH). Spectroscopic data consistent with those reported in the literature.[6]

Phenyl(2-(tributylstannyl)pyrrolidin-1-yl)methanone 50. Me_3SiI (0.71 mL, 5.0 mmol, 1.3 eq.) was added to a stirred solution of *N*-Boc stannyl pyrrolidine **49** (1.78 g, 3.9 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (6 mL) and CH_2Cl_2 (100 mL) were added and the two layers were separated. The organic layer was washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and then DMAP (47 mg, 0.39 mmol, 0.1 eq.), benzoyl chloride (0.49 mL, 4.3 mmol, 1.1 eq.) and Et_3N (0.81 mL, 5.8 mmol, 1.5 eq.) were added. The resulting solution was stirred at rt for 20 h. Then, $NaHCO_{3(aq)}$ (50 mL) and CH_2Cl_2 (50 mL) were added and the two layers were separated. The organic layer was washed with $NH_4Cl_{(aq)}$ (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 80:20 petrol-Et_2O as eluent gave pyrrolidine **50** (1.27 g, 70%) as a colourless oil, R_F (98:2 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2911, 2881, 1653 (C=O), 1526, 1427, 1380, 1342, 707, 623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.45 (m, 2H, Ph), 7.41-7.36 (m, 3H, Ph), 3.57 (t, J = 8.5 Hz, 1H, NCH), 3.50 (ddd, J = 11.0, 7.0, 4.5 Hz, 1H, NCH), 3.39 (dt, J = 11.0, 7.0 Hz, 1H, NCH), 2.26 (dquin, J = 12.5, 7.0 Hz, 1H, CH), 2.05-1.93 (m, 1H, CH), 1.93-1.77 (m, 2H, CH), 1.68-1.42 (m, 6H, CH_2), 1.32 (sextet, J = 7.5 Hz, 6H, CH_2Me), 0.97-0.91 (m, 6H, CH_2), 0.89 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8 (C=O), 137.3 (*ipso*-Ph), 129.5 (Ph), 128.2 (Ph), 127.1 (Ph), 50.1 (NCH_2), 47.7 (NCH), 29.6 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 13.8 (Me), 10.2 (CH_2); MS (ESI) *m/z* 466 [(M + H)$^+$, 100], 408 (70); HRMS (ESI) *m/z* calcd for $C_{23}H_{39}NOSn$ (M + H)$^+$ 466.2130, found 466.2122 (+1.1 ppm error).

2,2,2-Triphenyl-1-(2-(tributylstannyl)pyrrolidin-1-yl)ethanone 51. Me_3SiI (790 μL, 5.5 mmol, 1.3 eq.) was added to a stirred solution of *N*-Boc stannyl pyrrolidine **49** (1.97 g, 4.3 mmol, 1.0 eq.) in CH_2Cl_2 (32 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (6 mL) and CH_2Cl_2 (75 mL) were added and the two layers were separated. The organic layer was washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the deprotected stannyl pyrrolidine, which was sufficiently pure (by ^{1}H NMR spectroscopy) for use in the next step. In a separate flask, oxalyl chloride (870 mg, 580 μL, 6.8 mmol, 1.6 eq.) was added to a stirred suspension of triphenylacetic acid (1.36 g, 4.7 mmol, 1.1 eq.) in CH_2Cl_2 (8 mL) at rt under Ar. Then, DMF (1 drop) was added and the reaction mixture was stirred and heated at 35 °C for 2 h until a brown solution was formed and effervescence ceased. Then, the solvent was evaporated under reduced pressure to give a light brown solid. The solid was dissolved in CH_2Cl_2 (8 mL) and added to a stirred solution of the deprotected stannyl pyrrolidine (1.54 g, 4.3 mmol, 1.0 eq.) and DMAP (52 mg, 0.4 mmol, 0.1 eq.) in CH_2Cl_2 (50 mL) at rt under Ar. Then, Et_3N (1.29 g, 1.79 mL, 12.8 mmol, 3.0 eq.) was added and the reaction mixture was stirred at rt for 60 h. Then, saturated $NaHCO_{3(aq)}$ (15 mL) and CH_2Cl_2 (15 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude

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product. Purification by flash column chromatography on silica with 95:5 petrol-Et_2O as eluent gave stannyl pyrrolidine **51** (1.93 g, 71%) as a white solid, mp 121-123 °C; R_F (95:5 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2971, 2912, 1585 (C=O), 1470, 1424, 1379, 1196, 763, 731, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 6H, Ph), 7.23-7.16 (m, 9H, Ph), 3.68 (t, J = 8.5 Hz, 1H, NCH), 2.79 (ddd, J = 11.0, 7.0, 4.0 Hz, 1H, NCH), 2.29 (ddd, J = 11.0, 8.5, 6.5 Hz, 1H, NCH), 2.10-1.97 (m, 1H, CH), 1.80-1.69 (m, 1H, CH), 1.65-1.55 (m, 1H, CH), 1.55-1.40 (m, 7H, CH + CH_2), 1.31 (sextet, J = 7.5 Hz, 6H, CH_2Me), 1.00-0.82 (m, 6H, CH_2), 0.89 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.0 (C=O), 143.3 (*ipso*-Ph), 130.5 (Ph), 127.5 (Ph), 126.3 (Ph), 67.6 (*C*Ph_3), 49.6 (NCH), 48.7 (NCH_2), 29.3 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 27.6 (CH_2), 13.8 (Me), 10.4 (CH_2); MS (ESI) *m/z* 654 [(M + Na)$^+$, 100], 632 [(M + H)$^+$, 80]; HRMS (ESI) *m/z* calcd for $C_{36}H_{49}NOSn$ (M + H)$^+$ 632.2916, found 632.2891 (+2.9 ppm error).

2-(Tributylstannyl) *N*-(2,4,6-triisopropylphenylsulfonyl) pyrrolidine 52. Me_3SiI (467 µL, 3.25 mmol, 1.3 eq.) was added to a stirred solution of *N*-Boc stannyl pyrrolidine **49** (1.15 g, 2.5 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) at rt under Ar. The resulting solution was stirred at rt for 30 min. Then, water (6 mL) and CH_2Cl_2 (75 mL) were added and the two layers were separated. The organic layer was washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the deprotected stannyl pyrrolidine, which was sufficiently pure (by ^1H NMR spectroscopy) for use in the next step. The residue was dissolved in CH_2Cl_2 (29 mL) and 2,4,6-triisopropylsulfonyl chloride (832 mg, 2.75 mmol, 1.1 eq.), DMAP (30 mg, 0.25 mmol, 0.1 eq.) and Et_3N (769 mg, 1.04 mL, 7.5 mmol, 3.0 eq.) were added sequentially at rt under Ar. The resulting solution was stirred at rt for 20 h. Then, saturated $NaHCO_{3(aq)}$ (30 mL) and CH_2Cl_2 (30 mL) were added and the two layers were separated. The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 petrol-Et_2O as eluent gave sulfonyl pyrrolidine **52** (781 mg, 50%) as a colourless oil, R_F (98:2 petrol-Et_2O) 0.3; IR ($CHCl_3$) 2913, 2882, 2827, 1575, 1439, 1272, 1128, 1055, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H, Ar), 4.25 (septet, J = 7.0 Hz, 2H, ArC*H*), 3.48 (t, J = 7.5 Hz, 1H, NCH), 3.13 (dt, J = 10.0, 7.0 Hz, 1H, NCH), 3.03 (dt, J = 10.0, 7.0 Hz, 1H, NCH), 2.90 (septet, J = 7.0 Hz, 1H, ArC*H*), 2.30-2.13 (m, 1H, CH), 1.99-1.80 (m, 3H, CH), 1.61-1.46 (m, 6H, CH_2), 1.33 (sextet, J = 7.5 Hz, 6H, CH_2), 1.26 (d, J = 7.0 Hz, 6H, CHMe_2), 1.25 (d, J = 7.0 Hz, 6H, CHMe_2), 1.24 (d, J = 7.0 Hz, 6H, CHMe_2), 1.00-0.93 (m, 6H, CH_2), 0.91 (t, J = 7.5 Hz, 9H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.6 (*ipso*-Ar), 151.1 (*ipso*-Ar), 137.7 (*ipso*-Ar), 123.7 (Ar), 48.1 (NCH_2), 47.1 (NCH), 34.1 (Ar*C*H), 31.0 (CH_2), 29.4 (Me), 29.2 (CH_2), 27.6 (CH_2), 26.2 (CH_2), 25.0 (Me), 24.8 (Me), 23.6 (Me), 13.7 (Me), 10.0 (CH_2); MS (ESI) *m/z* 650 [(M + Na)$^+$, 40], 628 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{31}H_{57}NO_2SSn$ (M + H)$^+$ 628.3209, found 628.3206 (–0.5 ppm error).

Pyrrolidine-1,2-diylbis(phenylmethanone) 53. *n*-BuLi (210 µL of a 2.5 M solution in hexanes, 0.5 mmol, 1.0 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **50** (232 mg, 0.5 mmol, 1.0 eq.) in THF (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Then, methyl *p*-tolylsulfinate **17** (340 mg, 2.0 mmol, 2.0 eq.) was added. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Then, MeOH (1 mL), saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 petrol-EtOAc with 1% Et_3N as eluent gave pyrrolidine **53** (44 mg, 62%) as a white solid, mp 93-95 °C; R_F (1:1 petrol-EtOAc) 0.2; IR ($CHCl_3$) 2962, 2835, 1667 (C=O, ketone), 1598 (C=O, amide), 1553, 1400, 1208, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.06 (m, 2H, Ph), 7.65-7.57 (m, 3H, Ph), 7.54-7.48 (m, 2H, Ph), 7.45-7.39 (m, 3H, Ph), 5.72 (dd, J = 8.5, 5.0 Hz, 1H, NCH), 3.75 (dt, J = 10.5, 7.0 Hz, 1H, NCH), 3.63 (dt, J = 10.5, 6.5 Hz, 1H, NCH), 2.45-2.36 (m, 1H, CH), 2.09-1.90 (m, 3H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.3 (C=O), 169.7 (C=O), 136.6 (*ipso*-Ph), 135.6 (*ipso*-Ph), 133.5 (Ph), 130.3 (Ph), 128.9 (Ph), 128.8 (Ph), 128.4 (Ph), 127.5 (Ph), 61.2 (NCH), 49.9 (NCH_2), 29.2 (CH_2), 25.1 (CH_2); MS (ESI) *m/z* 302 [(M + Na)$^+$, 40], 280 [(M + H)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_2$ (M + H)$^+$ 280.1332, found 280.1329 (+1.2 ppm error).

2,2,2-Triphenyl-1-(pyrrolidin-1-yl)ethanone 55 and 2,2,2-Triphenyl-1-(5-(*p*-tolylsulfinyl)-2,3-dihydro-1H-pyrrol-1-yl)ethanone 56. *n*-BuLi (260 µL of a 2.5 M solution in hexanes, 0.65 mmol, 1.3 eq.) was added dropwise to a stirred solution of stannyl pyrrolidine **51** (315 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 min. Then, methyl *p*-tolylsulfinate **17** (128 mg, 0.75 mmol, 1.5 eq.) was added. The resulting solution was stirred at –78 °C for 10 min and then allowed to warm to rt over 1 h. Then, MeOH (0.5 mL), saturated $NH_4Cl_{(aq)}$ (5 mL) and Et_2O (5 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 1:1 petrol-EtOAc with 0.5% of Et_3N gave pyrrolidine **55** (74 mg, 43%) as a white solid, mp 175-177 °C (lit.,[41] 188.5 °C); R_F (7:3 petrol-EtOAc) 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (m, 15H, Ph), 3.66 (t, J = 6.5 Hz, 2H, NCH_2), 2.44 (t, J = 6.5 Hz, 2H, NCH_2), 1.72 (quin, J = 6.5 Hz, 2H, CH_2), 1.57 (quin, J = 6.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 142.9 (*ipso*-Ph), 130.5 (Ph), 127.7 (Ph), 126.6 (Ph), 54.8 (*C*Ph_3), 48.3 (NCH_2), 47.8 (NCH_2), 26.6 (CH_2), 23.2 (CH_2) and sulfoxide **56** (50 mg, 21%) as a white solid, mp 160-163 °C; R_F (1:1 petrol-EtOAc with 0.5% of Et_3N) 0.3; IR ($CHCl_3$) 2962, 1612 (C=O), 1363, 1212, 1020, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H, Ar), 7.27 (d, J = 8.0 Hz, 2H, Ar), 7.22-7.15 (m, 9H, Ar), 6.93-6.87 (m, 6H, Ar), 6.30 (dd, J = 3.5, 2.0 Hz, 1H, =CH), 3.45-3.37 (m, 1H, NCH), 2.67-2.42 (m, 2H, NCH and CH), 2.47 (s, 3H, Me), 2.41-2.29 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.7 (C=O), 152.3 (*ipso*-Ar), 142.3 (*ipso*-Ar), 141.7 (=C), 141.5 (*ipso*-Ar), 130.0 (Ar), 129.4 (Ar), 127.8 (Ar), 127.4 (Ar), 126.7 (Ar), 116.3 (=CH), 66.7 (*C*Ph_3), 51.7 (NCH_2), 29.4 (CH_2), 21.5 (Me); MS (ESI) *m/z* 500 [(M + Na)$^+$, 100], 478 [(M + H)$^+$, 50]; HRMS (ESI) *m/z* calcd for $C_{31}H_{27}NO_2S$ (M + H)$^+$ 478.1835, found 478.1855 (–4.4 ppm error). Spectroscopic data for **55** consistent with those reported in the literature.[41]

2,2-Dimethyl-1-(2-(*p*-tolylsulfinyl)azetidin-1-yl)propane-1-thione 58. *s*-BuLi (0.92 mL of a 1.3 M solution in hexanes,

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1.20 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-thiopivaloyl azetidine **57** (157 mg, 1.00 mmol, 1.0 eq.) and TMEDA (358 μL, 2.40 mmol, 2.4 eq.) in THF (6 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, methyl *p*-toluenesulfinate **17** (340 mg, 2.0 mmol, 2.0 eq.) and the solution was allowed to warm to rt over 2 h and stirred at rt for 16h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 91:9 mixture of diastereoisomers by ^{1}H NMR. Purification by flash column chromatography on silica with 8:2-1:1 petrol-EtOAc as eluent gave sulfoxide **58** (27 mg, 9%) as a colourless oil, R_F (7:3 petrol-EtOAc) 0.2; IR (film) 2987, 2954, 1502, 1480, 1424, 1395, 1240, 1140, 1025, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.32 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 5.55 (dd, J = 9.0, 4.5 Hz, 1H, NCH), 4.50 (dt, J = 9.0, 7.0 Hz, 1H, NCH_AH_B), 4.34 (dt, J = 9.0, 4.5 Hz, 1H, NCH$_A$$H_B$), 2.83 (ddt, J = 12.0, 9.0, 4.5 Hz, 1H, CH), 2.41 (s, 3H, Me), 2.06 (dtd, J = 12.0, 9.0, 7.0 Hz, 1H, CH), 1.39 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.5 (C=S), 141.3 (*ipso*-Ar), 137.3 (*ipso*-Ar), 129.9 (Ar), 123.9 (Ar), 86.0 (NCH), 56.5 (NCH_2), 43.8 (CMe_3), 29.7 (CMe_3), 21.3 (Me) 17.3 (CH_2); MS (ESI) *m/z* 318 [(M + Na)$^+$, 100], 296 [(M + H)$^+$, 50]; HRMS *m/z* calcd for $C_{15}H_{21}NOS_2$ (M + Na)$^+$ 318.0962, found 318.0960 (−0.5 ppm error) and recovered *N*-thiopivaloyl azetidine **57** (113 mg, 72%). Diagnostic signal for other diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dd, J = 9.0, 4.0 Hz, 1H, NCH).

***tert*-Butyl 1-(*p*-tolylsulfinyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate *syn*-60 and *anti*-60.** *s*-BuLi (2.11 mL of a 1.3 M solution in hexanes, 2.75 mmol, 2.2 eq.) was added dropwise to a stirred solution of *N*-Boc 4-chloro piperidine **59** (275 mg, 1.25 mmol, 1.0 eq.) and TMEDA (319 mg, 2.75 mmol, 2.2 eq.) in Et_2O (8 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Then, methyl *p*-toluenesulfinate **17** (468 mg, 2.75 mmol, 2.2 eq.) was added and the solution was allowed to warm to rt over 2 h and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 3:2 petrol-EtOAc with 1% Et_3N as eluent gave sulfoxide *syn*-**60** (142 mg, 35%) as a white solid, mp 161-163 °C; R_F (3:2 petrol-EtOAc) 0.3; IR ($CHCl_3$) 2975, 2931, 1703 (C=O), 1492, 1454, 1393, 1368, 1257, 1168, 1083, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H, *m*-C_6H_4Me), 7.28 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.47 (br s, 1H, NCH_AH_B), 2.84 (br s, 1H, NCH$_A$$H_B$), 2.41 (s, 3H, Me), 2.28 (br s, 1H, CH), 1.93-1.90 (m, 1H, CH), 1.77-1.74 (m, 2H, CH), 1.52 (br s, 9H, CMe_3), 1.16-1.13 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (rotamers) δ 155.0 (br, C=O), 141.9 (*ipso*-Ar), 141.6 (*ipso*-Ar), 141.1 (*ipso*-Ar), 139.5 (*ipso*-Ar), 129.7 (br, Ar), 125.5 (Ar), 124.8 (Ar), 81.2 (br, CMe_3), 61.2 (NCS(O)Ar), 61.1 (NCS(O)Ar), 52.3 (br, NCH_2), 28.5 (CMe_3), 26.1 (br, CH_2), 23.7 (CH_2), 22.3 (CH_2), 21.6 (Me), 11.9 (CH), 11.7 (CH); MS (ESI) *m/z* 344 [(M + Na)$^+$, 30], 322 [(M + H)$^+$, 100]; HRMS *m/z* calcd for $C_{17}H_{23}NO_3S$ (M + Na)$^+$ 344.1291, found 344.1286 (+1.5 ppm error) and sulfoxide *anti*-**60** (144 mg, 36%) as a colourless oil, R_F (3:2 petrol-EtOAc) 0.2; IR (film) 2977, 2932, 1696 (C=O), 1477, 1384, 1335, 1257, 1168, 1083, 1048, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 2H, *m*-C_6H_4Me), 7.26 (d, J = 8.0 Hz, 2H, *o*-C_6H_4Me), 3.79-3.72 (m, 1H, NCH_AH_B), 3.61 (br s, 1H, NCH$_A$$H_B$), 2.37 (s, 3H, Me), 2.27-2.18 (m, 1H, CH), 2.05 (dtd, J = 8.0, 7.0, 1.5 Hz, 1H, NCC*H*), 1.83-1.75 (m, 1H, CH), 1.49 (s, 9H, CMe_3), 1.09 (t, J = 7.0 Hz, 1H, CH), 1.05-1.01 (br m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.5 (C=O), 141.4 (*ipso*-Ar), 138.0 (*ipso*-Ar), 129.5 (Ar), 124.8 (Ar), 80.9 (CMe_3), 69.9 (br, NCS(O)Ar), 52.5 (br, NCH_2), 29.9 (br, CH_2), 28.4 (CMe_3), 26.8 (CH_2), 24.3 (br, CH), 21.3 (Me); MS (ESI) *m/z* 344 [(M + Na)$^+$, 40], 322 [(M + H)$^+$, 100]; HRMS *m/z* calcd for $C_{17}H_{23}NO_3S$ (M + Na)$^+$ 344.1291, found 344.1286 (+1.3 ppm error). Spectroscopic data consistent with those reported in the literature.[8]

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