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Synthesis of Enantiopure Piperazines *via* Asymmetric Lithiation-Trapping of *N*-Boc Piperazines: Unexpected Role of the Electrophile and Distal *N*-Substituent

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Supporting Information Placeholder

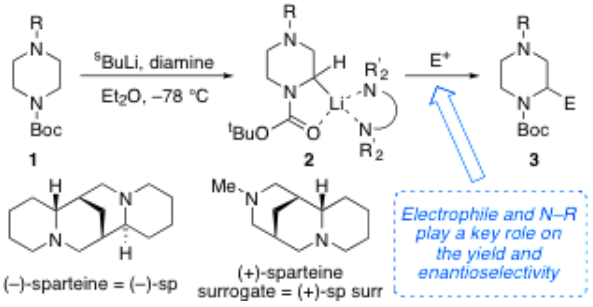
ABSTRACT: A new method for the synthesis of enantiopure α-substituted piperazines *via* direct functionalisation of the intact piperazine ring is described. The approach utilizes the asymmetric lithiation-substitution of an α-methylbenzyl-functionalised *N*-Boc piperazine using *s*-BuLi/(–)-sparteine or (+)-sparteine surrogate and provides access to a range of piperazines (as single stereoisomers). Optimization of the new methodology required a detailed mechanistic study. Surprisingly, it was found that the main culprits affecting the yield and enantioselectivity were the electrophile (the last reagent to be added to the reaction flask) and the distal *N*-substituent. The mechanistic studies included optimization of lithiation times using *in situ* IR spectroscopy, identification of a ring-fragmentation of the lithiated piperazines (that could be minimized with sterically hindered *N*-alkyl groups) and use of a novel "diamine-switch" strategy to improve enantioselectivity with certain electrophiles. The methodology was showcased with the preparation of an intermediate for Indinavir synthesis and the stereoselective synthesis of 2,5-*trans*- and 2,6-*trans*-piperazines.

Introduction

Piperazines occupy a privileged position in the development of small-molecule therapeutic agents. The piperazine motif is the third most frequent nitrogen heterocycle in ~2000 FDA-approved pharmaceuticals[1] and the fourth most common ring in drugs approved by the FDA between 1983 and 2012 (51 out of 1175 drugs contained piperazines).[2] There are examples of *α-substituted* piperazine drugs – Indinavir,[3] an antiretroviral drug used for the treatment of HIV and Vestipitant,[4] a NK-1 antagonist in clinical trials for the treatment of anxiety and tinnitus. However, such examples are rare mainly because of the lack of general routes to enantiopure α-substituted piperazines. The most common approaches are racemic synthesis coupled with classical resolution[5] (used to synthesise Indinavir[6] and Vestipitant[7]) and synthesis from α-amino acids typically proceeding *via* diketopiperazines.[8] More recent synthetic approaches have used a kinetic resolution process[9] or have started from α-amino acids and utilised Pd-catalysed cyclisation onto alkenes[10] or Mitsunobu chemistry.[11] A chiral reagent approach (RMgX/(–)-sparteine) was adopted in additions to pyrazine *N*-oxide,[12] and, in selected cases, chiral auxiliary[13] and chiral catalysis[14-16] have also been successful, although the methods deliver variable enantioselectivity. The most recent approaches generated α-substituted piperazines *via* Au catalysis,[17] SnAP reagents[18] and photoredox catalysis,[19] but, in general, racemic products were formed. All of the previous approaches suffer from one or two limitations: (i) the α-substituent is introduced at an early stage and (ii) they do not represent a general approach to enantiopure α-substituted piperazines. In this paper, we present an approach that solves both of these limitations and represents a practical, general asymmetric route to α-substituted piperazines *via* direct functionalisation of the intact piperazine ring.

The enantioselective α-functionalisation of *N*-Boc-protected nitrogen heterocycles *via* lithiation-trapping is one of the best methods for the synthesis of *enantioenriched* α-substituted nitrogen heterocycles.[20] Asymmetric α-lithiation-trapping of *N*-Boc pyrrolidine[21] and *N*-Boc piperidine[22] are well established and include applications in the synthesis of pharmaceuticals.[23] In contrast, there is only one example of the asymmetric lithiation of a *N*-Boc piperazine: McDermott at AstraZeneca[24] reported the α-lithiation-carboxylation of a *N*-Boc piperazine using *s*-BuLi/(–)-sparteine to give a trapped product (after amide formation) in 48% yield and 89:11 er.[25,26] Given the opportunity for the direct introduction of functionality, we set out to investigate this enantioselective approach to α-substituted piperazines. Lithiation of *N*-Boc piperazines **1** using *s*-BuLi and (–)-sparteine or the (+)-sparteine surrogate[27] would give either enantiomer of lithiated intermediates **2** which would be trapped to give α-substituted piperazines **3** (Scheme 1).

Scheme 1. Direct piperazine functionalisation approach to α-substituted piperazines.



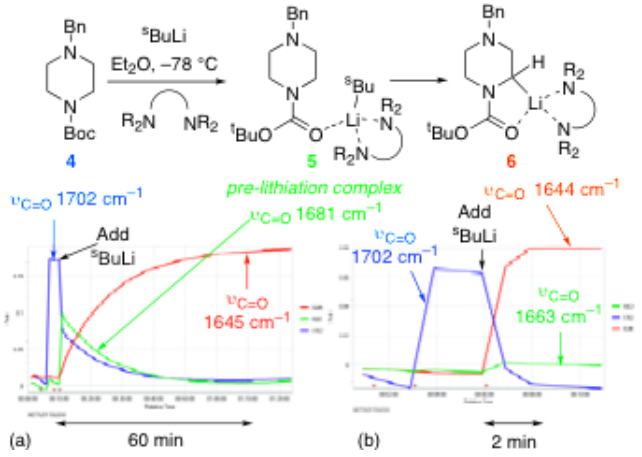
On paper, such an approach appears to be a simple extension of Beak's methodology. In practice, we discovered a number of issues to be resolved. Of note, and unexpectedly, the main culprits that affected the yield and enantioselectivity were the electrophile, the final reagent to be added to the reaction flask, and the distal nitrogen substituent (*N*-R in **1**) which is far away from the lithiation position. Our study also addresses a key limitation of *N*-Boc α-lithiation-trapping examples, namely the inability to deliver products in ≥99:1 er.[21-24,28] In this paper, we describe the mechanistic nuances of the optimization of the α-lithiation-trapping of *N*-Boc piperazines **1** and we exploit them in a new strategy for the stereoselective synthesis of either antipode of a range of *single stereoisomer* α-substituted piperazines **3**. This new strategy is showcased with applications such as preparation of an advanced intermediate for Indinavir synthesis and the stereoselective synthesis of 2,5-*trans*-/2,6-*trans*-piperazines.

Results and Discussion

Preliminary Results for the Enantioselective Lithiation-trapping of *N*-Boc Piperazine 4

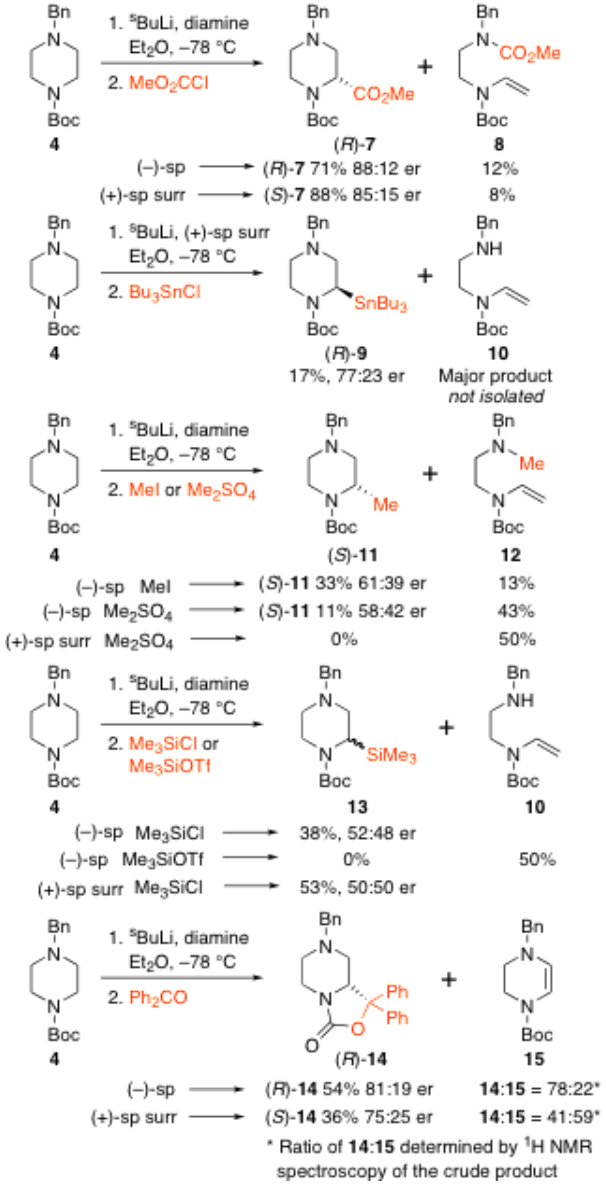
The starting point in our group for investigating the α-lithiation of a new *N*-Boc substrate is the use of *in situ* IR spectroscopy to identify the time taken for lithiation (by monitoring the change in $\nu_{C=O}$).[22c,29,30] Initially, the orthogonally protected *N*-Boc-*N*'-benzyl piperazine **4**[25f] was used. A solution of **4** (1.0 mmol) in Et_2O (14 mL) at –78 °C (in the presence of (–)-sparteine) exhibited a $\nu_{C=O}$ peak at 1702 cm^{-1}. On addition of *s*-BuLi, lithiation of **4** proceeded to give the organolithium **6** ($\nu_{C=O}$ peak at 1645 cm^{-1}); formation of a pre-lithiation complex **5**, assigned to a peak at 1681 cm^{-1}, was also observed (Scheme 2a, 2-D plot of absorbance *versus* time). As the reaction progressed, the proportion of both **4** and **5** decreased whilst that of the lithiated species **6** steadily increased (lithiation time ~60 min, $t_{1/2}$ ~9.5 min[31]). As seen with *N*-Boc pyrrolidine and *N*-Boc piperidine,[22c,29a] lithiation of **4** with *s*-BuLi/(+)-sparteine surrogate was an order of magnitude faster than that with (–)-sparteine: lithiation to give **6** (*via* **5**) occurred in 2 min ($t_{1/2}$ ~0.5 min Scheme 2b).

Scheme 2. *In situ* IR spectroscopic monitoring of the asymmetric lithiation of *N*-Boc piperazine 4: (a) *s*-BuLi/(–)-sparteine; (b) *s*-BuLi/(+)-sparteine surrogate.



With suitable lithiation times for **4** (Et_2O, –78 °C) in hand, we investigated a series of reactions, trapping with seven electrophiles: MeO_2CCl, Bu_3SnCl, MeI, Me_2SO_4, Me_3SiCl, Me_3SiOTf and Ph_2CO. These initial results are summarised in Scheme 3 and are, at first site, particularly discouraging – notably, the outcome of the reactions was strongly dependent on the electrophile, the last reagent to be added.

Scheme 3. Enantioselective lithiation-trapping of *N*-Boc piperazine 4.



The yields of the desired α-substituted piperazines **7**, **9**, **11**, **13** and **14** varied considerably (0-88%), and **7** was the only α-substituted product that was generated in >54% yield (trapping with MeO_2CCl). The low yields could in general be accounted for by the generation of two distinct types of alkene-containing by-products. With MeO_2CCl, Bu_3SnCl, MeI, Me_2SO_4, Me_3SiCl and Me_3SiOTf, vinyl carbamates **8**, **10** and **12** were formed (to differing extents) *via* a piperazine ring-fragmentation process (with functionalisation of the nitrogen by the electrophile and, in the cases with silicon- or tin-based electrophiles, subsequent cleavage of the labile *N*–Si and *N*–Sn bonds to give **10**). In contrast, with Ph_2CO, the only by-product generated was unsaturated piperazine **15**. Furthermore, the enantioselectivity was also electrophile-

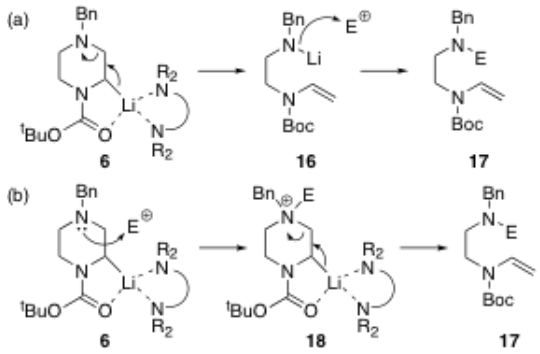
dependent. With MeO_2CCl, Bu_3SnCl and Ph_2CO, products (*R*)-/(*S*)-**7**, **9** and **14** were formed in 75:25-88:12 er whereas lower enantioselectivity was observed when trapping with MeI, Me_2SO_4 or Me_3SiCl (50:50-61:39 er). The configuration of **7**, **9**, **11** and **14** was assigned by analogy with McDermott's precedent with *s*-BuLi/(–)-sparteine.[24]

From the results shown in Scheme 3, three key aspects required explanation: (i) formation of the ring-fragmentation by-products **8**, **10** and **12**; (ii) the low enantioselectivity observed using MeI, Me_2SO_4 and Me_3SiCl (→ **11**/**13**); (iii) formation of unsaturated piperazine **15** and the accompanying moderate enantioselectivity in the formation **14** upon trapping with Ph_2CO. To explain each of these, we have identified three distinct mechanistic processes and addressing each of these provided the focus for optimising the α-lithiation-trapping of *N*-Boc piperazines and, ultimately, the development of a new strategy to enantiopure piperazines.

Addressing piperazine ring-fragmentation: lithiation-trapping of sterically hindered *N*-Boc piperazines

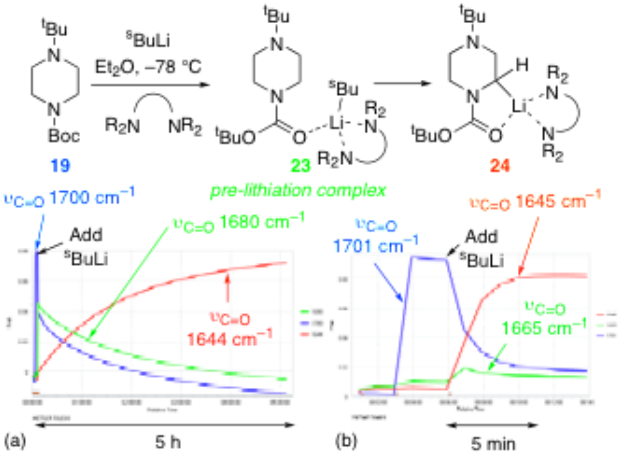
Initially, we considered formation of the ring-fragmentation by-products **8**, **10** and **12**. A potential mechanism would be ring-fragmentation *via* β-elimination of the *N*-alkyl group from lithiated piperazine **6** to give vinyl carbamate **16** which could then trap on nitrogen to give the observed products **17** (with *N*–Sn and *N*–Si bond cleavage → **10** in those examples) (Scheme 4a). Such a mechanism is precedented with substituted morpholines[32] (alkoxide leaving group) and a *N*-Boc-*N*-phenyl piperazine[33] (anilide leaving group).[34] However, the mechanism in Scheme 4a would not explain the electrophile-dependence of the results presented in Scheme 3[35] and the fact that ring-fragmentation has not been observed in racemic lithiation-trappings of *N*-alkyl-*N*-Boc piperazines with the electrophiles in Scheme 3.[25,26] Hence, we propose an alternative mechanism for ring-fragmentation in which the order of the two steps is reversed so that the ligands around the lithium can play a key role (Scheme 4b). Since the lithiated piperazine **6** has a sterically hindered diamine ligand ((–)-sparteine or the (+)-sparteine surrogate) coordinated to the lithium, we wondered whether the nucleophilic *N*-alkyl substituent could competitively react with the electrophile. This would generate ammonium ion intermediates **18** which, now equipped with a good leaving group, would readily β-eliminate to give vinyl carbamates **17**. Although this mechanism appears speculative, there is some precedent for amines reacting with electrophiles in preference to enolates in amine-containing enolates.[36]

Scheme 4. Mechanistic proposals for ring-fragmentation in the enantioselective lithiation-trapping of *N*-Boc piperazine 4.



If our mechanistic conjecture in Scheme 4b was correct then increasing the steric hindrance around the *N*-alkyl group should lead to a reduction in ring-fragmentation and accordingly higher yields of the desired α-substituted piperazines. To investigate this, *N*-Boc piperazines **19**-**22** with four sterically hindered groups (*t*-butyl, trityl, 9-phenylfluoren-9-yl (PhFl) and cumyl) were prepared and the lithiation of a representative substrate, *N*-Boc-*N'*-*t*-butyl piperazine **19** was studied using *in situ* IR spectroscopy (Scheme 5). Since the *N*-alkyl group is far from the lithiation site, we expected similar lithiation times to those with *N*-Boc-*N*'-benzyl piperazine **4**. Surprisingly, the distal *N*-*t*-butyl group slowed down the rate of lithiation considerably. Using *s*-BuLi/(–)-sparteine, conversion of *N*-Boc-*N'*-*t*-butyl piperazine **19** ($\nu_{C=O}$ peak at 1700 cm^{-1}), *via* pre-lithiation complex **23** ($\nu_{C=O}$ peak at 1680 cm^{-1}), to lithiated piperazine **24** ($\nu_{C=O}$ peak at 1644 cm^{-1}) was almost complete after 5 h with $t_{1/2}$ ~60 min (Scheme 5a). The corresponding *N*-benzyl piperazine **4** was lithiated in 60 min (see Scheme 2a). Similarly, the *s*-BuLi/(+)-sparteine surrogate lithiation of *N*-Boc-*N'*-*t*-butyl piperazine **19** (lithiation time: 5 min, $t_{1/2}$ ~1 min Scheme 5b) took longer than that of *N*-benzyl piperazine **4** (lithiation time: 2 min, see Scheme 2a). These differences could perhaps be due to a change in conformation of the piperazine or aggregation effects of the *s*-BuLi/diamine complex.

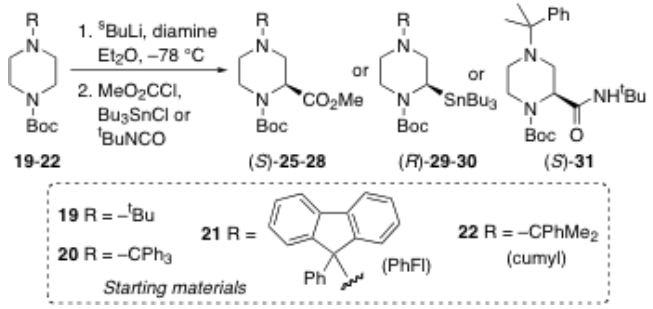
Scheme 5. *In situ* IR spectroscopic monitoring of the asymmetric lithiation of *N*-Boc piperazine 19: (a) *s*-BuLi/(–)-sparteine; (b) *s*-BuLi/(+)-sparteine surrogate.



The *in situ* IR spectroscopic study directed us to lithiation times of 6 h (for (–)-sparteine) and 1 h (for the (+)-sparteine surrogate) for the α-lithiation-trapping of *N*-Boc piperazines containing the sterically hindered groups (Table 1). Using MeO_2CCl, Bu_3SnCl and *t*-BuNCO as electrophiles, no ring-

fragmentation by-products were observed in the ^{1}H NMR spectra of the crude products and good yields of trapped products (*R*)- or (*S*)-**25**-**31** were obtained. This should be compared with the results using *N*-benzyl piperazine **4** (MeO_2CCl or Bu_3SnCl) where ring-fragmentation occurred (see Scheme 3), supporting our proposed mechanism for ring-fragmentation (see Scheme 4b). Of the four *N*-alkyl groups investigated, the trityl and PhFl groups gave the lowest enantioselectivity (entries 3, 4 and 7). The *t*-butyl and cumyl groups gave similar yields and ers (compare entries 1/5 and 2/6) but we could not remove the *t*-butyl group. Our preferred *N*-alkyl group is thus cumyl (*N*-Boc-*N*-cumyl piperazine **22**) as it gave trapped products in high yields and enantioselectivity with both diamines. For example, using the (+)-sparteine surrogate, substituted piperazines (*S*)-**28** (83%, 88:12 er, entry 6) and (*S*)-**30** (99%, 86:14 er, entry 9) were generated. The cumyl group could be readily removed using transfer hydrogenolysis: reaction of (*S*)-**28** with $Pd(OH)_2$/C and $NH_4^+HCO_2^-$ gave the free amine (97% yield). Subsequent Cbz protection and ester hydrolysis then gave a known[37] compound and this allowed the absolute configuration to be confirmed (see Supporting Information). Thus, elucidation of a mechanism for piperazine ring-fragmentation highlighted a key role for the distal *N*-alkyl group. Ultimately, use of the sterically hindered *N*-cumyl group allowed high yielding asymmetric α-lithiation-trapping of *N*-Boc piperazines to be developed.

Table 1. Enantioselective lithiation-trapping of sterically hindered *N*-Boc piperazines 19-22.



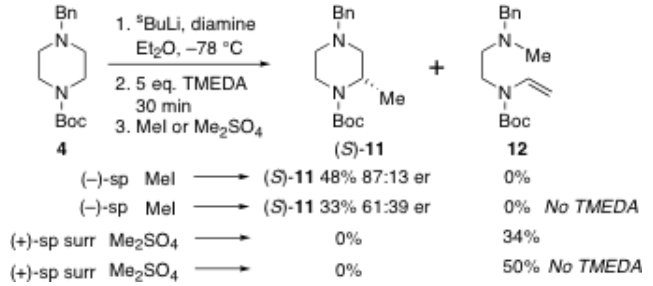
Entry	SM[a]	R	Electrophile	Prod[b]	Yield/%[c]	Er[d]
1	**19**	*t*-Bu	MeO_2CCl	(*R*)-**25**[e]	72	89:11
2	**19**	*t*-Bu	MeO_2CCl	(*S*)-**25**[f]	90	89:11
3	**20**	CPh_3	MeO_2CCl	(*S*)-**26**[f]	81	81:19
4	**21**	PhFl	MeO_2CCl	(*S*)-**27**[f]	68	84:16
5	**22**	Cumyl	MeO_2CCl	(*R*)-**28**[e]	71	90:10
6	**22**	Cumyl	MeO_2CCl	(*S*)-**28**[f]	83	88:12
7	**20**	CPh_3	Bu_3SnCl	(*R*)-**29**[f]	74	82:18
8	**22**	Cumyl	Bu_3SnCl	(*S*)-**30**[e]	61	88:12
9	**22**	Cumyl	Bu_3SnCl	(*R*)-**30**[f]	99	86:14
10	**22**	Cumyl	*t*-BuNCO	(*S*)-**31**[f]	54	87:13

[a] Starting material. [b] Product. [c] % Yield after chromatography. [d] Enantiomer ratio determined using CSP-HPLC (see Supporting Information). [e] Diamine = (–)-sp, lithiation time = 6 h. [f] Diamine = (+)-sp surr, lithiation time = 1 h.

Addressing low enantioselectivity with certain electrophiles: the "diamine switch" strategy

Next, we considered the fact that α-substituted piperazines **11** and **13** were generated in very low ers (50:50-61:39 er) using MeI, Me_2SO_4 and Me_3SiCl (see Scheme 3). These results are reminiscent of results with *N*-Boc pyrrolidine[38] and *N*-Boc piperidine.[22c] In these cases, sterically hindered ligands around the lithium (*e.g.* (–)-sparteine and the (+)-sparteine surrogate) and slow-trapping electrophiles led to poor enantioselectivity. This is because trapping of the lithiated *N*-Boc heterocycle is slow at –78 °C and only took place at temperatures at which the lithiated *N*-Boc heterocycle was configurationally unstable. Piperazines appeared to be particularly prone to this problem and, in order to address it, we devised a "diamine switch" strategy. The idea was to switch the sterically hindered chiral diamine for the less sterically hindered TMEDA ligand *after the lithiation event*. It was hoped that this would allow a more efficient trapping[39] at temperatures where the lithiated *N*-Boc piperazine was configurationally stable (typically below –40 °C[22c,40]). The results of this study, trapping with MeI or Me_2SO_4, are shown in Scheme 6.

Scheme 6. Investigation of a "diamine switch" strategy.

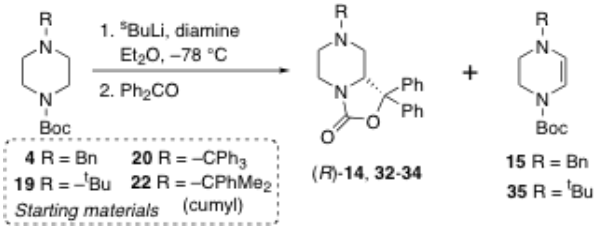


Lithiation of *N*-Boc-*N*-benzyl piperazine **4** using *s*-BuLi/(–)-sparteine in Et_2O at –78 °C was followed by addition of 5 eq. TMEDA (–78 °C, 30 min). Then, in the expectation that TMEDA had displaced the (–)-sparteine, MeI was added. This delivered methylated piperazine (*S*)-**11** in 48% yield and 87:13 er. Without the "diamine switch" step, (*S*)-**11** was formed in 61:39 er and 33% yield (see Scheme 3). Furthermore, no piperazine ring-fragmentation was detected using the "diamine switch" protocol (without TMEDA, 13% of ring-fragmentation product **12** was formed). Clearly, adding TMEDA had a significant effect on the outcome of the reaction, which we believe is due to the sterically hindered (–)-sparteine being displaced by TMEDA which then allows trapping to occur at lower temperatures where the organolithium is configurationally stable.[41] Disappointingly, a similar "diamine switch" with the (+)-sparteine surrogate failed: trapping with Me_2SO_4 gave ring-fragmentation product **12** only (34% yield). Presumably, TMEDA did not displace the (+)-sparteine surrogate from the lithiated piperazine and ring-fragmentation (*via* the mechanism outlined in Scheme 4b) ensued. This result is in line with our previous observation of the better coordinating power of the (+)-sparteine surrogate compared to (–)-sparteine and THF.[42]

Investigating the formation of unsaturated piperazine 15 and reduced enantioselectivity with Ph_2CO: the SET mechanism

The results with Ph_2CO shown in Scheme 3 gave a different profile to the other electrophiles: a different alkene by-product, unsaturated piperazine **15**, was formed and the enantioselectivity of the trapped product **14** was moderate (75:25-81:19 er) but definitely lower than that of the MeO_2CCl-trapped ester **7** (85:15-88:12 er). To account for both of these observations, we believe that a single electron transfer (SET) mechanism is also operating when trapping with Ph_2CO.[43] One electron oxidation of lithiated *N*-Boc piperazine **5** by Ph_2CO would give an α-amino radical and the radical anion of Ph_2CO. The α-amino radical could either lose a β-hydrogen atom to give **15** or trap the Ph_2CO radical anion to give some racemic **14** (ultimately lowering the er of **14**). Based on the appreciable er of **14** observed (75:25-81:19 er), it appears that the SET Ph_2CO trapping process is only a minor pathway. To investigate the SET pathway, we explored a range of reactions of different *N*-Boc piperazines using (–)-sparteine and the (+)-sparteine surrogate (Table 2).

Table 2. Enantioselective lithiation-trapping of *N*-Boc piperazines 4, 19, 20 and 22 using Ph_2CO.



Entry	SM[a]	R	Prod[b]	Yield/ %[c]	Er[d]	Prod: Alkene[e]
1	**4**	Bn	(*R*)-**14**[f]	54	81:19	78:22[g]
2	**4**	Bn	(*S*)-**14**[h]	36	75:25	41:59[g]
3	**19**	*t*-Bu	(*R*)-**32**[f]	74	90:10	100:0
4	**19**	*t*-Bu	(*S*)-**32**[h]	76	86:14	85:15[i]
5	**20**	CPh_3	(*S*)-**33**[h]	80	73:27	100:0
6	**22**	Cumyl	(*R*)-**34**[f]	53	91:9	100:0
7	**22**	Cumyl	(*S*)-**34**[h]	73	87:13	100:0

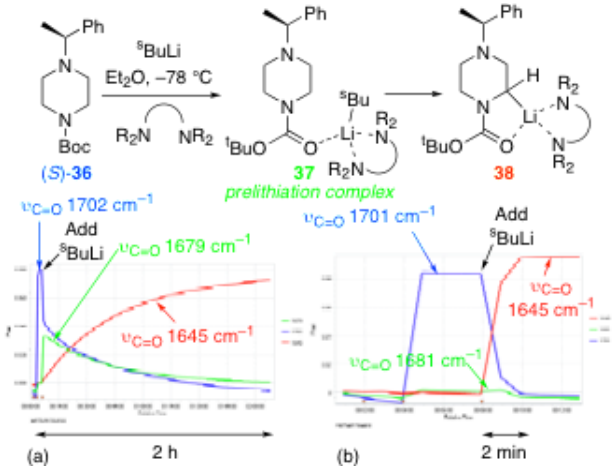
[a] Starting material. [b] Product. [c] % Yield after chromatography. [d] Enantiomer ratio determined using CSP-HPLC (see Supporting Information). [e] Ratio of product:alkene **15** or **35** determined by ^{1}H NMR spectroscopy of the crude product. [f] Diamine = (–)-sp, lithiation time = 6 h. [g] By-product = alkene **15**. [h] Diamine = (+)-sp surr, lithiation time = 1 h. [i] By-product = alkene **35**.

Some trends emerge from the results shown in Table 2. For example, for **4** and **19**, a higher proportion of alkenes **15** and **35**, respectively, were observed with (+)-sparteine surrogate compared to (–)-sparteine (compare entries 1/2 and 3/4). This suggests that more of the SET process occurs with the (+)-sparteine surrogate. In general, a more sterically hindered *N*-alkyl group led to less alkene by-product and use of the cumyl group (*N*-Boc-*N*-cumyl piperazine **22**) gave the best results in terms of enantioselectivity (87:13-91:9 er) and the fact that no alkene by-product was observed (entries 6/7). Since the SET mechanism is only an issue with Ph_2CO as the electrophile, it was not studied further. However, the potential for lower ers and alkene by-products should be appreciated when trapping with Ph_2CO.

Synthesis of enantiopure α-substituted piperazines: use of an α-methylbenzyl *N*-alkyl group

The remaining issue to be addressed was the stereoselective preparation of *enantiopure* α-substituted piperazines. With this in mind, we realised that it was necessary to have a sterically hindered *N*-alkyl group to stop ring-fragmentation. In addition, building on the initial work of Guerrini and coworkers,[44] use of a stereogenic α-methylbenzyl *N*-alkyl group would allow separable, diastereomeric α-substituted piperazines to be generated upon trapping. Our innovation is the use of a chiral diamine to dictate the major diastereomer that would be formed. Adapting a literature route,[45] piperazine (*S*)-**36** was readily synthesised on a multi-gram scale in three steps (74% overall yield) from commercial materials (only one chromatographic purification). To ascertain suitable lithiation times, *in situ* IR spectroscopy was utilised. A solution of (*S*)-**36** in Et_2O at –78 °C (in the presence of (–)-sparteine) exhibited a $\nu_{C=O}$ peak at 1702 cm^{-1}. On addition of *s*-BuLi, lithiation of (*S*)-**36** gave organolithium **38** ($\nu_{C=O}$ peak at 1645 cm^{-1}) *via* pre-lithiation complex **37** ($\nu_{C=O}$ peak at 1679 cm^{-1}) (Scheme 7a). Lithiation of (*S*)-**36** to give lithiated piperazine **38** neared completion only after 2 h ($t_{1/2}$ ~26 min). Of note, this lithiation is slower than that of *N*-Boc-*N*'-benzyl piperazine **4** (see Scheme 2a), presumably due to extra steric hindrance of the distal *N*-alkyl group. In contrast, lithiation of (*S*)-**36** with *s*-BuLi/(+)-sparteine surrogate was much faster: (*S*)-**36** gave **38** in 2 min ($t_{1/2}$ ~0.5 min, Scheme 7b).

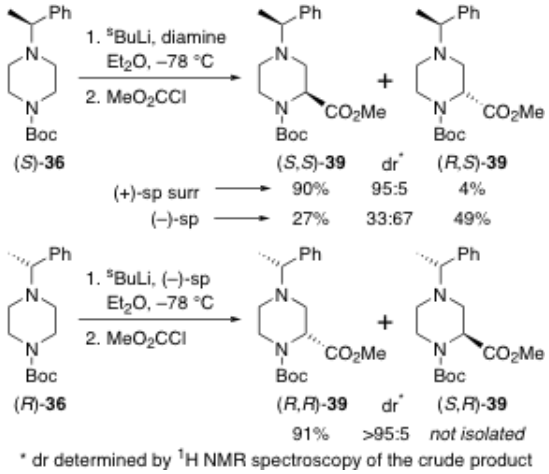
Scheme 7. *In situ* IR spectroscopic monitoring of the asymmetric lithiation of *N*-Boc piperazine (*S*)-36: (a) *s*-BuLi/(–)-sparteine; (b) *s*-BuLi/(+)-sparteine surrogate.



Next, we explored the diastereoselectivity of the lithiation of (*S*)-**36** using the (+)-sparteine surrogate and (–)-sparteine. Guided by *in situ* IR spectroscopy, lithiation of (*S*)-**36** using *s*-BuLi/(+)-sparteine surrogate in Et_2O at –78 °C was carried

out for 10 min. Subsequent trapping with MeO_2CCl delivered a 95:5 mixture of diastereomeric piperazines (*S*,*S*)-**39** and (*R*,*S*)-**39** (by ^{1}H NMR spectroscopy of the crude product) (Scheme 8). The diastereomers were readily separable and, after purification, piperazine (*S*,*S*)-**39** was obtained in 90% yield ((*R*,*S*)-**39** isolated in 4% yield). However, the corresponding reaction of (*S*)-**36** with *s*-BuLi/(–)-sparteine (3 h lithiation time) was less satisfactory as a 67:33 mixture of (*R*,*S*)-**39** and (*S*,*S*)-**39** was produced (Scheme 8). Given that we already knew that steric hindrance at the *N*-alkyl group could affect the rate of lithiation (see Schemes 2, 5 and 7), we speculated that a long-range match/mismatch effect between the α-methylbenzyl group and the Boc-coordinated *s*-BuLi/chiral diamine complex could occur to account for these differing outcomes. Two experiments were deployed to confirm this: (i) lithiation-trapping of (*S*)-**36** using *s*-BuLi/TMEDA gave a 68:32 mixture of (*S*,*S*)-**39** and (*R*,*S*)-**39** clearly showing that there was an inherent substrate preference[44,46] and (ii) lithiation-trapping of enantiomeric (*R*)-**36** using *s*-BuLi/(–)-sparteine gave a >95:5 mixture of (*R*,*R*)-**39** and (*S*,*R*)-**39** from which a 91% yield of (*R*,*R*)-**39** was obtained (Scheme 8). Thus, by matching the configuration of the α-methylbenzyl group with that of the chiral diamine, high yields of piperazines (*S*,*S*)-**39** (90%) and (*R*,*R*)-**39** (91%) (as single stereosiomers) can be obtained by the direct functionalisation of piperazines (*S*)-**36** or (*R*)-**36**. Of note, no ring-fragmentation products were observed in these reactions, due to the presence of the sterically hindered *N*-alkyl group. The α-methylbenzyl in (*S*,*S*)-**39** could be readily removed upon treatment with Pd/C and hydrogen$^-$ for further functionalisation; Cbz protection and ester hydrolysis gave a known[37] piperazine, confirming the configuration.

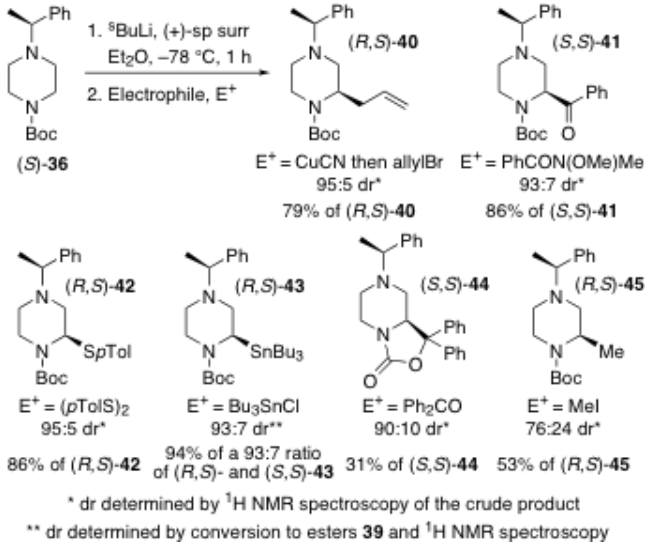
Scheme 8. Investigation of the diastereoselectivity in the lithiation-trapping of *N*-Boc piperazine (*S*)-36.



* dr determined by ^{1}H NMR spectroscopy of the crude product

A range of electrophiles (allyl–Br, Weinreb amide, Bu_3SnCl, $(pTolS)_2$, Ph_2CO and MeI) was then explored using (*S*)-**36** and lithiating with *s*-BuLi/(+)-sparteine surrogate (Scheme 9). In general, diastereoselectivity was high (90:10-95:5 dr) and allowed high isolated yields of single stereoisomeric piperazines to be obtained: allylated (*R*,*S*)-**40** (79%), ketone (*S*,*S*)-**41** (86%) and sulfide (*R*,*S*)-**42** (86%). With Bu_3SnCl, an inseparable 93:7 mixture of diastereomeric stannanes (*R*,*S*)-**43** and (*S*,*S*)-**43** was isolated (94%). However, in line with previously described results, Ph_2CO and MeI gave problems and these led to lower yields of (*S*,*S*)-**44** (31%) and (*R*,*S*)-**45** (53%) respectively. In the case of Ph_2CO, significant quantities of a dihydropyrazine alkene by-product were observed in the crude reaction mixture which is indicative of a competing SET pathway. The SET pathway can also probably account for the slightly lower 90:10 dr in this case.

Scheme 9. Electrophile scope in the lithiation-trapping of *N*-Boc piperazine (*S*)-36.

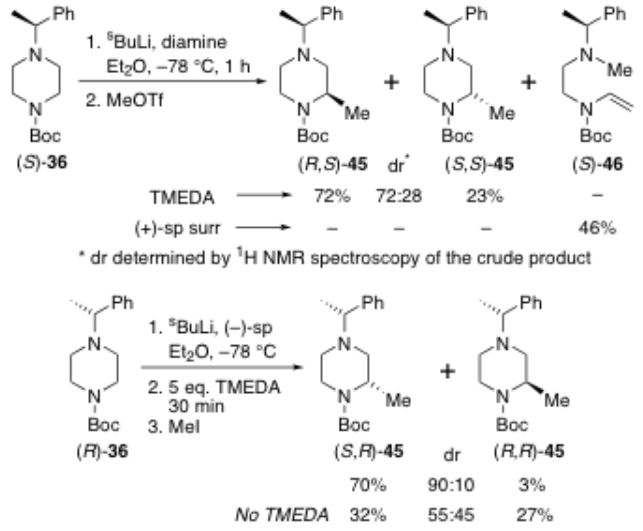


* dr determined by ^{1}H NMR spectroscopy of the crude product

** dr determined by conversion to esters **39** and ^{1}H NMR spectroscopy

With MeI, lower diastereoselectivity likely resulted from slow trapping at –78 °C so that trapping took place at temperatures where the lithiated *N*-Boc piperazine is configurationally unstable. Two approaches were explored to improve the methylation yield. First, a more reactive electrophile, MeOTf, was investigated with the intention that it would trap at lower temperatures before configurational instability of the lithiated piperazine became an issue. With *s*-BuLi/TMEDA and trapping with MeOTf, a 72:28 mixture of (*R*,*S*)-**45** and (*S*,*S*)-**45** was generated which gave a 72% yield of methylated (*R*,*S*)-**45** after chromatography (Scheme 10). However, attempted improvement of the diastereoselectivity using *s*-BuLi/(+)-sparteine surrogate failed completely: we only observed ring-fragmentation and (*S*)-**46** was isolated in 46% yield.[47] As noted earlier, use of the more sterically hindered ligand around the lithium impedes the desired trapping and ring-fragmentation occurs (*via* methylation of the *N*-alkyl amine). Nevertheless, the combination of TMEDA and MeOTf delivered our best yield of methylated (*R*,*S*)-**45** (72%). Second, a "diamine switch" strategy was explored. Based on previous results with *N*-Boc-*N*'-benzyl piperazine **4** (see Scheme 6), we focused on (–)-sparteine and started with its matched piperazine (*R*)-**36**. After lithiation of (*R*)-**36** with *s*-BuLi/(–)-sparteine, 5 eq. TMEDA was added and reaction with MeI gave a 90:10 mixture of (*S*,*R*)-**45** and (*R*,*R*)-**45**. The major diastereomer, (*S*,*R*)-**45**, was isolated in 70% yield (Scheme 10). Without the "diamine switch", diastereoselectivity was particularly low (55:45 dr), clearly highlighting the slower rate of trapping when (–)-sparteine is complexed to the lithium rather than TMEDA.

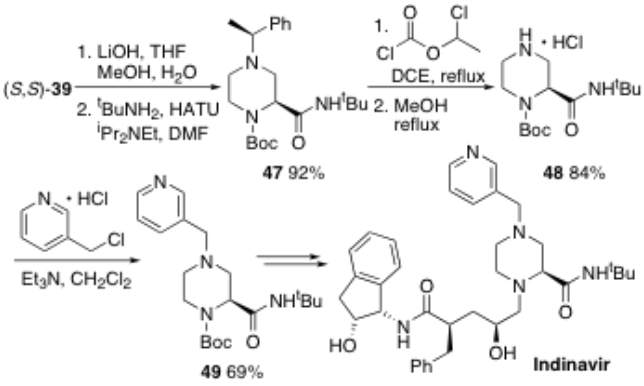
Scheme 10. Investigation of the use of MeOTf and a "diamine switch" strategy.



Synthetic applications of single stereoisomer piperazines

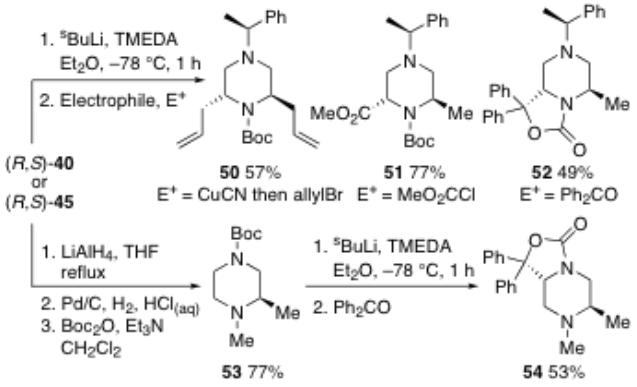
With readily available piperazines as single stereosiomers in hand, we set out to demonstrate the synthetic utility of our new methodology. Methyl ester (*S*,*S*)-**39** was first converted into amide **47** by ester hydrolysis and amide formation. Then, the α-methylbenzyl group was deprotected using α-chloroethyl chloroformate[48] to give **48**. Alkylation of **48** then generated piperazine **49**, a suitably functionalised building block equipped for application in the synthesis of Indinavir.

Scheme 11. Synthesis of an advanced intermediate for the synthesis of Indinavir.



Finally, we have also used the single stereoisomeric piperazines in the synthesis of functionalized, disubstituted piperazines. Routes from allylated (*R*,*S*)-**40** and methylated (*R*,*S*)-**45** to 2,6-*trans*- and 2,5-*trans*-disubstituted piperazines *via* a second α-lithiation-trapping were developed (Scheme 12). Lithiation-allylation of allylated (*R*,*S*)-**40** delivered **50** in which the *trans*-stereochemistry was established by α-methylbenzyl group removal (see Supporting Information) to give a chiral amine ($[\alpha]_D$ –34.9 (*c* 0.7, $CHCl_3$)).[49] In a similar way, methylated (*R*,*S*)-**45** gave methyl ester **51** and oxazolidinone **52** after trapping with MeO_2CCl and Ph_2CO respectively. Presumably, *trans* diastereoselectivity to give **50**, **51** or **52** results from an axially disposed allyl or methyl group (to avoid $A^{1,3}$ strain with the Boc group), equatorial lithiation and retentive electrophilic trapping.[50,51] The high yield (77%) of **51** suggests that the two *N*-Boc rotamers readily interconvert at –78 °C as was observed with *N*-Boc 2-phenyl piperidine.[29b] Alternatively, translocation of the Boc group in methylated (*R*,*S*)-**45** to the other nitrogen (*via* $LiAlH_4$ reduction, hydrogenolysis and Boc protection) gave **53** which was α-lithiated and trapped to form 2,5-*trans*-disubstituted piperazine **54**. The regiochemistry is due to steric hindrance and the diastereoselectivity arises from an equatorial methyl group in **19** and equatorial lithiation/retentive trapping.[50]

Scheme 12. Stereoselective synthesis of enantiopure 2,6-*trans*- and 2,5-*trans*-piperazines.



Conclusion

In summary, a new, practical method for the stereoselective synthesis of enantiopure piperazines *via* direct functionalisation of the intact piperazine ring is described. Our approach addresses the two key limitations of previous routes to α-substituted piperazines. As typical examples, the one-step functionalisation of piperazines (*S*)-**36** or (*R*)-**36** to give single stereoisomers of methyl esters (*S*,*S*)-**39** (90% yield) or (*R*,*R*)-**39** (91% yield) respectively serve to illustrate the potential of the methodology. The success of the strategy relied on the use of a stereogenic α-methylbenzyl group and the realisation that a sterically hindered *N*-alkyl group reduced the likelihood of ring-fragmentation of the lithiated piperazine. The optimisation process revealed that the electrophile, the last reagent to be added, affected the yield and enantio-/diastereoselectivity and mechanisms were proposed to explain these effects. In addition, our studies have also implicated the *N*-alkyl group and the diamine ligand around the lithium as other factors that affected yield and enantio-/diastereoselectivity. With (–)-sparteine, the use of a new "diamine switch" strategy can improve enantio-/diastereoselectivity with slow trapping electrophiles such as MeI. Our comprehensive mechanistic study also included identification of lithiation times using *in situ* IR spectroscopy. Ultimately, the utility of the new methodology was demonstrated by the concise synthesis of an advanced intermediate for Indinavir synthesis and of 2,5-*trans*- and 2,6-*trans*-disubstituted piperazines.

ASSOCIATED CONTENT

Supporting Information. Full experimental procedures and spectroscopic data, copies of NMR spectra, *in situ* IR spectroscopic data and CSP-HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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31. In this paper, we determine $t_{1/2}$ values from the emergence of the lithiated species (**6** in Scheme 2, **24** in Scheme 5 and **38** in Scheme 7) and the $t_{1/2}$ value is defined as the time taken for the absorbance to reach half of its maximum value.

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34. To probe the mechanism proposed in Scheme 4a, we generated lithiated *N*-methyl-*N*-Boc piperazine (a substrate we had found to be particularly prone to ring-fragmentation) using *s*-BuLi/THF at –78 °C for 1 hour and then incubated the organolithium intermediate at 0 °C for 1 hour. After quenching with saturated $NH_4Cl_{(aq)}$, only starting material was recovered (quantitatively); no ring-fragmentation products were detected.

35. The effect of excess electrophile on the ring-fragmentation process has been explored in one example: *N*-Boc-*N'*-benzyl piperazine **4** was lithiated using *s*-BuLi/(–)-sparteine and trapped with MeO_2CCl (10 eq.) to give α-substituted piperazine (*R*)-**7** in 40% yield and ring-fragmentation by-product **8** in 36% yield (see Supporting Information). This should be compared to the use of 2 eq. MeO_2CCl which gave a 71% yield of (*R*)-**7** and a 12% yield of **8** (see Scheme 3). Clearly, the ring-fragmentation process is favoured by a large excess of electrophile, a result that is inconsistent with the mechanism in Scheme 4a and supports our preference for the mechanism depicted in Scheme 4b. From a synthetic viewpoint, use of large excesses of electrophile should be avoided if α-substituted products are targeted.

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41. The added TMEDA (5 eq.) in these examples may exert its influence in other ways, such as by coordinating to other lithiated intermediates that are generated (including lithium iodide).

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46. Lithiation of (*S*)-**39** using *s*-BuLi/TMEDA and trapping with MeO_2CCl was complicated by formation of a disubstituted piperazine. This occurs *via* enolate formation and Claisen reaction during the trapping step and will likely have affected the ratio of (*S*,*S*)- and (*R*,*S*)-**39**.

47. Methylation of a lithiated piperazine coordinated by the (+)-sparteine surrogate appears particularly problematic and ring-fragmentation is the dominant pathway with MeI, Me_2SO_4 and MeOTf (see **12** in Schemes 2 and 6; see (*S*)-**46** in Scheme 10).

48. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

49. A *meso* amine would have been produced if the piperazine had *cis*-stereochemistry. This synthesis of **50** and proof of *trans*-stereochemistry suggest that a related *cis*-selective reaction has been assigned incorrectly (see reference 25a).

50. For related examples with piperidines, see: Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

51. Schanen, V.; Cherrier, M.; Sebastião, J.; Quirion, J.; Husson, H. *Synthesis* **1996**, 833.

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