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Enantioselective carbolithiation of *S*-alkenyl-*N*-aryl thiocarbamates: kinetic and thermodynamic control

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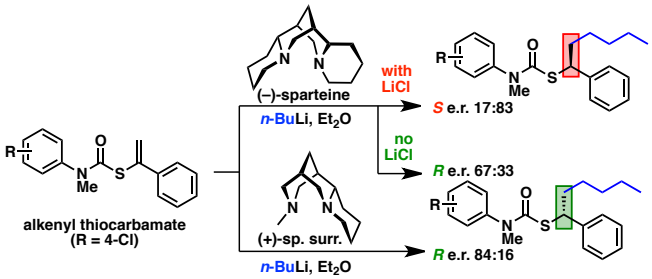
Abstract: The addition of *n*-butyllithium to alkenylthiocarbamates in the presence of (–)-sparteine or the (+)-sparteine surrogate leads to asymmetric carbolithiation, and returns enantiomerically enriched thiocarbamate derivatives of secondary thiols. In THF, with the (+)-sparteine surrogate, in situ aryl migration leads to an enantiomerically enriched tertiary thiol derivative. Remarkably, the two pseudoenantiomeric chiral ligands do not always give enantiomeric products, probably as a result of a complex interplay of kinetic and thermodynamic control. In situ IR and NMR studies of a stable, hindered lithiated thiocarbamate demonstrated its chemical and configurational stability over a period of hours at 0 °C.

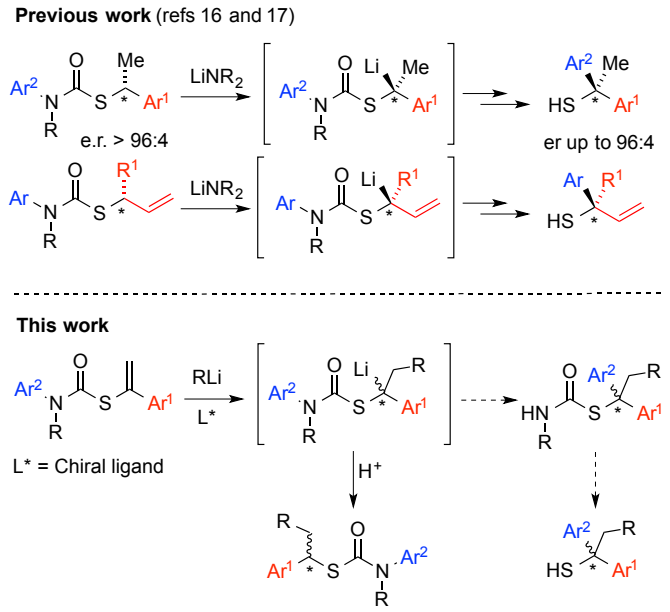


Introduction

The enantioselective synthesis of stereogenic centres carrying sulfur represents a challenge in synthetic chemistry. Approaches used for the synthesis of enantiopure alcohols and amines typically employ asymmetric reactions of C=O or C=N bonds with nucleophiles,[1-5] but corresponding strategies for the synthesis of sulfur compounds using C=S bonds represent a challenge.[6] As a result, some relatively simple families of sulfur-containing compounds are of limited synthetic accessibility.[7] The asymmetric synthesis of secondary thiols and their simple derivatives is generally achieved by stereospecific substitution of chiral electrophilic precursors.[6] For tertiary thiols,[7] Hoppe's thiocarbamate chemistry,[8-14] despite its attendant limitations of electrophiles, and the enantioselective palladium-catalyzed sigmatropic rearrangement of *O*-allyl thiocarbamates developed by Overman, are effective.[15] We recently reported some effective methods for the enantioselective synthesis of tertiary thiols based on lithiation/aryl migration sequences of S-benzyl-[16] and S-allyl[17,18] *N*-arylthiocarbamates (Scheme 1). The methods involve the generation of enantiomerically enriched configurationally stable organolithiums by deprotonation of chiral non racemic *S*-benzyl or *S*-allyl *N*-arylthiocarbamates: the organolithiums undergo stereospecific aryl migration[19] from the thiocarbamate N atom to the C atom α to S. In parallel, in the racemic series, we showed that the Li-coordinating abilities of the thiocarbamate group[8,11] could be exploited for a connective stereoselective synthesis of thiols by a diastereoselective carbolithiation of S-alkenyl groups followed by intramolecular N to C migration of an aryl moiety.[20] Carbolithiation of *S*-alkenyl *N*-arylthiocarbamates with a variety of organolithium reagents, leading to thiocarbamates and sulfur containing quaternary and tertiary stereocentres, occurred stereoselectively in several cases.

The development of an equivalent *asymmetric* carbolithiation[21,22] of *S*-alkenyl *N*-arylthiocarbamates could expand the portfolio of connective synthetic strategies leading

to enantioenriched tertiary thiols (Scheme 1). Building on the relatively limited number of previous reports of enantioselective carbolithiations,[23-30] we report the first asymmetric carbolithiations of alkenyl thiocarbamates. Using the chiral diamine ligands, such as (–)-sparteine and O'Brien's (+)-sparteine surrogate,[31-33] we demonstrate the formation of enantioenriched thiocarbamates from achiral substrates. In addition, we show the remarkable effect of the additive LiCl[34] on the stereochemical course of these reactions.



Scheme 1. Stereoselective strategies for the synthesis of enantiomerically enriched tertiary thiols.

Results and discussion

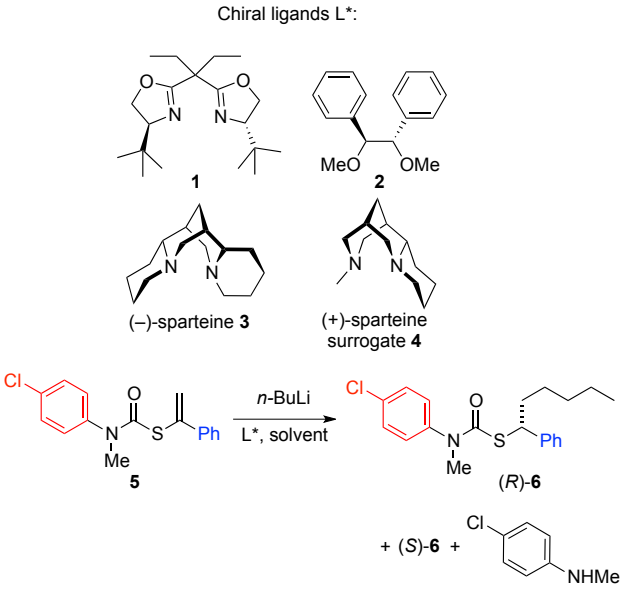
We started our investigation by evaluating the carbolithiation of *S*-alkenyl *N*-arylthiocarbamate **5** in the presence of chiral lithium-coordinating ligands **1-4**, and the results are collected in Table 1. Compound **5**, prepared according to a reported procedure,[20] was selected as a reference substrate due to the known facility of N to C aryl migrations of the 4-chlorophenyl group in lithiated thiocarbamates[16] and their congeners. [19,3536]

(–)-Sparteine **3**, the first ligand of choice for asymmetric organolithium chemistry,[37] was explored first (*entries 1-3*). A freshly prepared mixture of the complex of **3** with *n*-BuLi was treated with **5**, under several different reaction conditions, to give (after protonation) carbolithiated product **6** and variable amounts of *N*-methyl-4-chloroaniline as side product. When the reaction was carried out in Et_2O or cumene at -78 °C product (*R*)-**6** was obtained in 67:33 e.r. (entries 1, 4-5), while at higher temperature **6** was formed as an essentially racemic mixture (*entries 2-3*). Longer or shorter reaction times led to no improvement of the enantiomeric ratio. Treatment of **5** with the complex **3**-*n*-BuLi in toluene for 1 h, followed by the addition of DMPU (which usually promotes aryl migration, as well as racemization[19,35] [36]) still led to **6** (*entry 6*), again in racemic form. Treatment of **5** with the complex of bis-oxazoline **1** and *n*-BuLi at –78 °C afforded **6** in 60:40 er, or 51:49 e.r. at –30 °C (*entries 7-8*). Using **2** as a ligand gave only racemic material (*entry 9*).

Better enantioselectivity was obtained when **5** was treated with the complex of (+)-sparteine surrogate **4**[31-33] and *n*-BuLi complex (*entry 10*). The carbolithiated product (*R*)-**6** was obtained in 84:16 er, remarkably with the same sense of enantioselectivity as when (–)-sparteine was used. The higher enantioselectivity observed with **4** may be a result of the ability of **4** to give tighter complexes with organolithiums than **3**, but as far as we are aware the observation of the same sense of enantioselectivity from (–)-sparteine and the (+)-sparteine surrogate is unprecedented. Almost as surprisingly, enantioselectivity was also reversed when, in an attempt to promote rearrangement of the intermediate organolithium, LiCl was added[36] to the asymmetric carbolithiation induced by (–)-sparteine **3** (*entry 11*): carbolithiation of **5** in the presence of LiCl and (–)-sparteine **3** at -78 °C led to compound (*S*)-**6** in 83:17 er (entry 11). Nevertheless, compound **6** was obtained throughout in low yields mainly due to the formation of the side reaction product *N*-methyl-*p*-Cl-aniline as consequence of the attack of BuLi on the carbonyl group.

Absolute configuration was assigned by comparison of the CD spectrum and $[\alpha]_D$ values of the material produced from entries 10 and 11 with those of thiocarbamates of known configuration (see SI). Nonetheless, this assignment does imply that thiocarbamates undergo carbolithiation in the presence of **4** with the opposite sense of asymmetric induction when compared with ureas.[23] The sense of (–)-sparteine-directed enantioselective carbolithiation of carbamates depends on the organolithium. [26]

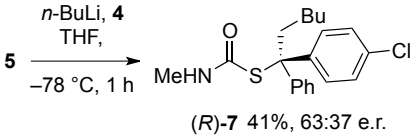
Table 1. Asymmetric carbolithiations of **5**



entry	*T* /°C	time	solvent	ligand	**6** yield /%[a]	e.r.[b] (*R*)-**6**:(*S*)-**6**
1	-78	1 h	Et_2O	**3**	33	67:33
2	-60	1 h	Et_2O	**3**	35	47:53
3	-78 to -30	16 h	Et_2O	**3**	24	48:52
4	-78	1 h	cumene	**3**	36	66:34
5	-78	5 min.	cumene	**3**	36	67:33
6	-78	2h[c]	tol, DMPU	**3**	18	50:50
7	-78	3h	Et_2O	**1**	35	60:40
8	-30	3h	Et_2O	**1**	37	51:49
9	-78	1h	Et_2O	**2**	32	50:50
10	**-78**	**1h**	**Et_2O**	**4**	**31**	**84:16**[e]
11	**-78**	**4h**	**Et_2O**	**3/LiCl**[d]	**49**	**17:83**[e]

[a]Yields of isolated product **6**. [b]Established by HPLC analysis on chiral stationary phase. [c]0.1 mmol of **5** in 0.4 mL of toluene were treated with BuLi-**3** complex and stirred for 1h at –78 °C. DMPU (0.1 mL) was added and the resulting mixture was stirred at -78 °C for 1h. [d]10 equiv of LiCl were used. [e]Absolute configuration determined by comparison of CD spectrum and $[\alpha]_D$ values with those of related compounds.

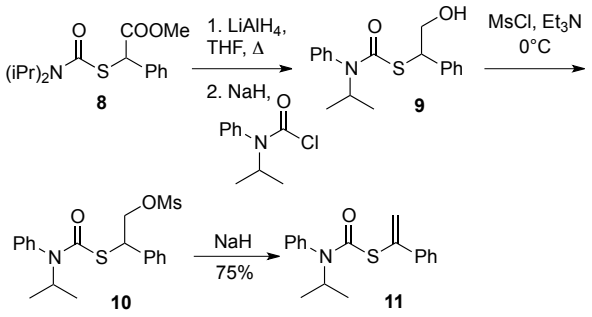
Unusually among lithium-complexing ligands, the (+)-sparteine surrogate is competitive with THF as a ligand for Li^+, and can induce enantioselectivity even in reactions carried out in THF solution. [38] When **5** was treated with the complex of **4** and *n*-BuLi in THF, aryl migration followed directly from the carbolithiation step and thiocarbamate **7** was isolated in 41% yield and in 63:37 e.r. (Scheme 2).[39] As noted before,[23] THF promotes the aryl migration, possibly by assisting decomplexation of Li^+ from either or both of the thiocarbamate C=O or the anionic C atom, leading to a solvent-separated ion pair.[40,41] However, as previously observed with DMPU, [36] this effect of THF also seems to lead to partial epimerization of the lithiated intermediate, lowering the er of the rearranged products.



(*R*)-**7** 41%, 63:37 e.r.

Scheme 2. Enantioselective carbolithiation-rearrangement in THF

Aiming to improve the yield and enantioselectivity of the carbolithiation reaction, and to explore on a simpler and better behaved system the erratic enantioselectivities obtained in these reactions, we decided to replace the *N*-methyl group of **5** with the more sterically hindered *N*-isopropyl group, reasoning that this would obstruct attack of *n*-BuLi on the thiocarbamate carbonyl group.[42] The *N*-isopropyl thiocarbamate **11**[20] was prepared by the synthetic route shown in Scheme 3. Thiocarbamate **8**, made by the method of Hoppe,[8] was reduced to the thiol with $LiAlH_4$ and acylated with *N*-isopropyl-*N*-phenylcarbamoyl chloride to give compound **9**. Mesylation to give **10** and NaH-promoted elimination afforded the *S*-alkenyl *N*-isopropylthiocarbamate **11**.



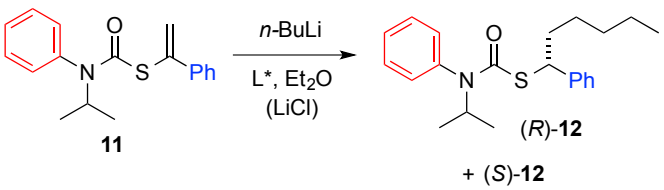
Scheme 3. Synthesis of a more hindered thiocarbamate

The thiocarbamate **11** was carbolithiated with *n*-BuLi in the presence of ligands L* **2-4**

(Table 2). No carbolithiation was observed in the presence of (–)-sparteine at –78 °C (*entry 1*) but at –50 °C (*R*)-**12** was obtained after quenching, in 60:40 e.r. and high yield (*entry 2*). Adding LiCl to this reaction led to the formation of **12** as a more or less racemic mixture after 3 h at –50 °C (*entry 3*). However, on increasing the temperature to 0 °C before quenching after 4 h, (*S*)-**12** was formed in 38:62 e.r. (*entry 4*). Despite the low yield (23%) of product **12** (due to decomposition of the lithiated intermediate at higher temperature) this result is remarkable because it demonstrates again the ability of LiCl to invert the configuration of the carbolithiation product formed using **3**. Comparing *entries 2-4* in Table 2 indicates that this inversion must arise after carbolithiation has taken place, suggesting that the effect is a result of LiCl promoting epimerization from a first-formed complex in which (*R*)-**12Li** predominates to a thermodynamically more stable complex in which (*S*)-**12Li** predominates.

When (+)-sparteine surrogate **4** was used as ligand, (*R*)-**12** was obtained in 70:30 er, both at -78 °C (where yield was compromised by the presence of 55% remaining starting material) and at -50 °C (entries 5 and 6). Ligand **2** was once more found to be ineffective, giving **12** in 56:44 e.r. (*entry 7*).

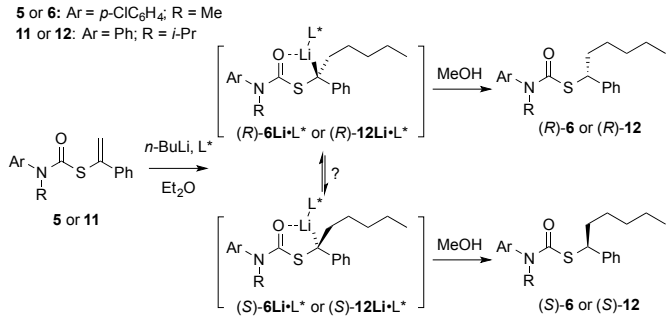
Table 2. Carbolithiation reactions of **11** in the presence of chiral lithium coordinating ligands



entry	T °C	time	additive	ligand	**12** yield /%[a]	e.r.[b] (*R*)-**12**:(*S*)-**12**
1	-78	1h	-	**3**	0	-
2	-50	1h	-	**3**	74	60:40
3	-50	3h	LiCl	**3**	61	47:53
4	**-78 to 0**	**4h**	**LiCl**	**3**	**23**	**38:62**
5	-78	1h	-	**4**	28[c]	70:30
6	**-50**	**1h**	**-**	**4**	**62**	**69:31**
7	-50	1h	-	**2**	72	56:44

[a]Yields of isolated product **12**. [b]Established by HPLC analysis on chiral stationary phase. Configuration assigned by analogy with **6** [c] Starting material **11** was recovered (55%)

Tables 1 and 2 both display some remarkable results with common features. Firstly, they show that **3** and **4**, despite being pseudoenantiomeric, may give products with the same absolute stereochemistry. Secondly, they show that the 'enantiomeric' functions of **3** and **4** may be restored by adding LiCl to carbolithiation reactions induced by **3**: thus **3**+LiCl, but not **3** alone, behaves like the enantiomer of **4**. Consideration of the two possible mechanisms by which enantioselectivity may be induced in these processes allows us to propose two reaction pathways, illustrated in Scheme 4. In the first pathway, kinetic control induces facial selectivity in the addition step to give a configurationally stable organolithium **6Li•L*** or **12Li•L***, whose stereospecific protonation yields enantiomerically enriched compounds. In the second pathway, the addition step may or may not be enantioselective, but thermodynamic control over the equilibration of the resulting diastereoisomeric complexed organolithiums **6Li•L*** or **12Li•L*** gives enantiomerically enriched products, again by stereospecific protonation.



Scheme 4: Pathway for reaction via diastereoisomeric organolithium complexes.

Based on these considerations, we propose that the enantioselectivity observed in the carbolithiation of thiocarbamates **5** and **11** with **3** alone can be explained by assuming that the addition step occurs with some degree of face selectivity, and that the resulting α-thiobenzyllithiums are configurationally stable. [8,16,20] On protonation, (*R*)-**6** and (*R*)-**12** are obtained as the major enantiomers. The enantioselectivity switch, in the presence of **3** and LiCl, may be rationalized by assuming that LiCl weakens the interaction between the lithium cation and either or both of the carbonyl O and the anionic C atoms – an effect seen with THF or DMPU – and thus induces thermodynamically-controlled equilibration of the lithiated adducts, as illustrated in Figure 1. The diastereoisomeric lithiated intermediates A and D represent respectively the kinetic and thermodynamic favored complexes. In the presence of LiCl (**L** in Figure 1), formation of a solvent-separated ion pair B would allow equilibration, perhaps via a conducted tour mechanism, to C and hence to the more stable diasteromeric complex D. The contrasting behaviour of **4**, which gives the opposite enantiomer to **3** + LiCl in every case, could be explained by assuming that the tighter coordination between the organolithium **6Li** or **12Li** and **4** leads directly to the product of thermodynamic control without the need for an additive. Equilibration between the diastereoisomeric complexes **6Li•4** or **12Li•4** is faster than addition, and only the product ratio arising from thermodynamic control is observed.

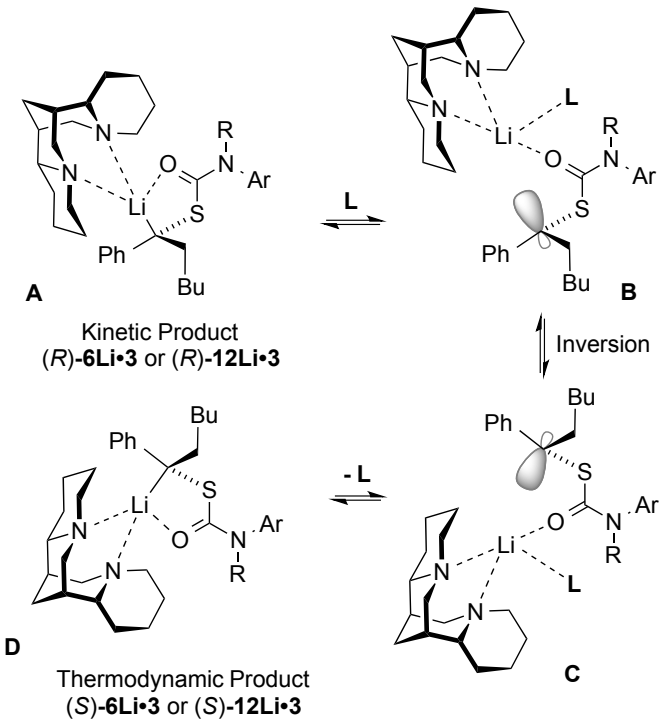
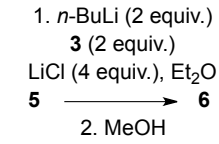


Figure 1 Pathway for equilibration between diastereoisomeric organolithium complexes.

A series of experiments was designed to test this hypothesis (Table 3). Thiocarbamate **5** was carbolithiated at -78 °C using a freshly prepared complex of (–)-sparteine **3** and *n*-BuLi in the presence of an excess (4 equiv) of LiCl. Reactions were stopped by quenching with MeOH at different times, in order to follow the progress of any thermodynamic equilibration. After 30 min. (*R*)-**6** was obtained in 57:43 e.r. (Table 3, *entry 1*); after 1 h a racemic mixture was detected (Table 3, *entry 2*). After 2 h the enantiomer (*S*)-**6** was in excess (33:67, entry 3)

and after 4 h the final e.r. of 17:83 in favour of (*S*)-**6** was reached (Table 3, *entry 4*). Carrying out the reaction for longer time led to no further increase in the e.r. Increasing the temperature increased the apparent rate of epimerization, so that even after 1 h at –40 °C, (*S*)-**6** was the major enantiomer (entry 5).

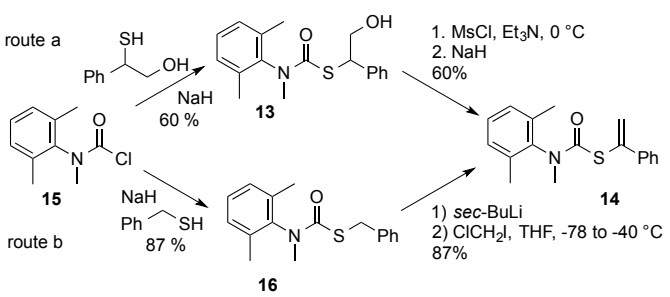
Table 3. Equilibration of the complex of **6Li** and **3** in the presence of LiCl



entry	T °C	time	**6** yield%[a]	er[b] (*R*)-**6**:(*S*)-**6**
1	-78	30 min	27	57:43
2	-78	1 h	22	50:50
3	-78	2 h	30	33:67
4	-78	4 h	49	17:83
5	-40	1 h	30	41:59

[a]Yields of isolated product **6**. [b]Established by HPLC analysis on chiral stationary phase.

Further insight into the reaction pathway would be available from spectroscopic studies (in-situ FT-IR, NMR) of the organolithium intermediates. However, yields in all of the reactions of **5** were compromised by competing formation of *N*-methyl-4-chloroaniline as a side product, probably from a combination of competing attack at the carbonyl group by *n*-BuLi and decomposition of the intermediate organolithium. Likewise, because **11** was carbolithiated only at high temperatures, competitive aryl migration also led to mixtures of products. We thus sought a cleanly reacting substrate suitable for spectroscopic studies. The reactivity of thiocarbamate **14,** designed as a hybrid of **5** and **11** and bearing a bulky N-aryl group, was therefore explored. This system could allow the optimization of the carbolithiation reaction without a competitive aryl migration, or the poor yields and poor reactivity seen at -78 °C. Compound **14** was initially prepared from carbamoyl chloride **15** following the synthetic approach used for **11** (Scheme 5, route a), and then also by a shorter and more efficient approach starting from **15** and benzyl thiol. Lithiation of **16** with *s*-BuLi and reaction with chloroiodomethane furnished thiocarbamate **14** in a high yielding single step methylenation (Scheme 5, route b). [43]

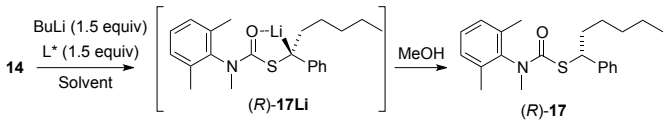


Scheme 5. Synthesis of thiocarbamate 14

The results of asymmetric carbolithiation of **14** in the presence of (–)-sparteine **3** and (+)-sparteine surrogate **4** are summarized in Table 4. As expected the carbolithiation reaction proceeded in very good yields even at low temperature and no trace of migration product or aniline derivative was detected. However, carbolithiation in the presence of (–)-sparteine **3** gave almost racemic samples of **17** under several reaction conditions (entries 1-3). Neither solvent nor temperature affected the stereoselectivity, which remained constant with reaction time (entries *4-5*). Likewise there was no change in enantioselectivity in the presence of LiCl as an additive (*entry 6*), even after longer reaction times or with a warm-cool protocol (*entries 7, 8*).

On the other hand, when (+)-sparteine surrogate **4** was used as ligand in Et_2O or toluene an appreciable degree of stereoselectivity was observed (*entries 9, 10*). A lower, but still measurable, degree of stereoselectivity was also observed using **4** in THF (*entry 8*). In both cases the (*R*)-**17** enantiomer was obtained as the major product, as it was (marginally) when (–)-sparteine was used. For sake of comparison, and based on a protocol developed by Hoppe and coworkers for the dynamic thermodynamic resolution of lithiated *S*-benzyl thiocarbamates,[8] the carbolithiation of **14** was performed in the presence of bis-oxazoline ligand **1**. Only racemic adduct was recovered (Table 4, entry 12).

Table 4. Carbolithiation of **14** in the presence of **3** or **4**



entry	solvent	T /°C	time (h)	additive	L*	**17** yield %[a]	er[b] (*R*)-**17**:(*S*)-**17**
1	Et_2O	–78	1	-	**3**	88	57:43
2	toluene	–78	1	-	**3**	87	57:43
3	cumene	–78	1	-	**3**	82	51:49
4	Et_2O	–98	0.15	-	**3**	88	51:49
5	Et_2O	–78 - –45 - –78[c]	1 - 18		**3**	85	53:47
6	Et_2O	–78	1	LiCl[d]	**3**	87	52:48
7	Et_2O	–78	4	LiCl[d]	**3**	84	50:50
8	Et_2O	–78 - 0 - –78[c]	4	LiCl[d]	**3**	78	51:49
9	**Et_2O**	**–78**	**1**	**-**	**4**	**80**	**70:30**
10	**toluene**	**–78**	**1**	**-**	**4**	**80**	**70:30**
11	THF	–78	1	-	**4**	78	63:36
12	Et_2O	–78 - –45 - –78[c]	18	-	**1**	88	52:48

[a]Yields of isolated product. [b]established by HPLC analysis on chiral stationary phase. [c]A warm/cooling protocol was applied. Conditions: addition of BuLi at –78 °C and after 1h the reaction mixture is warmed to -45 °C and left overnight. The reaction was cooled to –78 °C before quenching. [d]10 equiv LiCl added.

The progress of the carbolithiation of **14** was investigated by *in situ* FT-IR experiments carried out using a diamond ATR probe and monitoring the C=O stretching of thiocarbamate **14**. A 0.1 M toluene solution of **14** and ligand **4** (1.5 equiv) showed the stretching band of the C=O bond at 1680 cm^{-1} at -78 °C (Figure 2). Upon addition of *n*-BuLi a new signal, which we ascribe to the lithiated intermediates (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li**, was observed at lower wavenumber (1590 cm^{-1}), probably as a result of coordination between Li and the C=O group. [41,44-47] Quenching with deuterated methanol restored the signal for the C=O (1670 cm^{-1}) of the thiocarbamate **17-D** (Figure 2). Similar behaviour was noticed in the experiment carried out in the presence of (–)-sparteine **3**. The IR analysis revealed that the addition of *n*-BuLi occurs very quickly with both ligands **3** and **4**. Nevertheless, a careful analysis of the reaction profiles showed that the carbolithiation is slightly faster in the presence of **3** with respect to **4**: 80% of **14** was consumed in 30 sec in the presence of **3** and in 1 min in the presence of **4** (see supporting information).

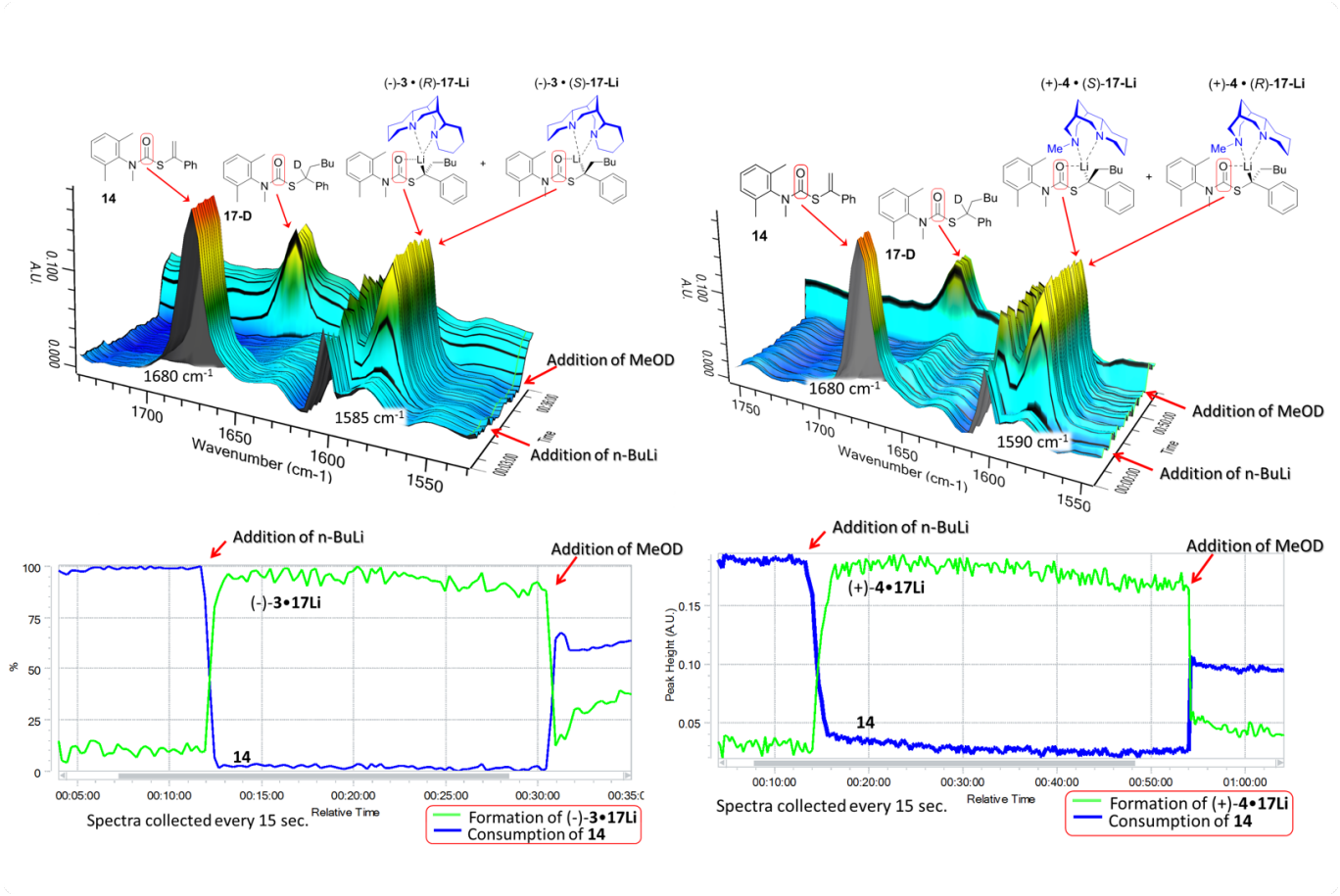


Figure 2. FT-IR monitoring of the enantioselective carbolithiation of **14** in the presence of ligands **3** and **4**.

The IR spectra give no evidence with regard to stereoselectivity or the existence of diastereoisomeric complexes, so the carbolithiation of **14** was also performed in an NMR tube, acquiring ^{1}H- and ^{13}C-NMR spectra. Running the carbolithiation reaction in the NMR tube at 200 K in d_8-toluene and in the presence of (+)-sparteine surrogate **4**, two

diastereomeric species were detected by ^{1}H NMR. The reaction reached completion as soon as **14** was added to a pre-cooled (–78 °C) 0.05 M solution of **4**-BuLi complex (1.5 equiv) in agreement with the results of the IR experiments. In particular, the aromatic region of the ^{1}H NMR spectra revealed two sets of signals belonging to diastereomeric complexes (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li** in a 70:30 ratio (Figure 3). Such signals appeared separately in the range 6.50 – 6.70 ppm and were unambiguously assigned, by HSQC-DEPT hetero-correlation experiments, to the *para* protons of the phenyl ring linked to the lithiated carbon. Figure 3 also shows the aromatic region (110 – 190 ppm) of the ^{13}C NMR spectrum observed for the diastereomeric mixture of (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li**. However, probably as a result of the low sample concentration, only the signals of the major lithiated intermediate are detectable. In particular, by comparison of the ^{13}C NMR chemical shifts of (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li** with those reported for a similar lithiated benzylic thiocarbamate by Hoppe, [8] we can confidently assign the NC=O (ca 184 ppm), the C_i (ca 153 ppm) and the C_p (ca 110 ppm) signals (Figure 3).

The lithiated intermediates (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li** generated in the NMR tube were deuterated with CD_3OD to give the corresponding deuterated product (>95% D) **17D** with an er of 75:25 (HPLC). This evidence lends support to the hypothesis that the signals observed by NMR belong to the two diastereomeric lithiated intermediates (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li**. In addition, the shielding observed for both protons H_p and carbon C_p and the deshielding for the carbon C_i, is in agreement with an increased charge density in the aromatic ring directly bonded to the lithiated carbon. Further NMR evidence for the structure of the organolithium generated by carbolithiation was the deshielding of the carbonyl group (NC=O, ca 184 ppm) that probably arises from intramolecular coordination of the lithium cation. This conclusion is also supported by the FT-IR exeperiments.

The same experiment was perfomed using (–)-sparteine **3** as the chiral ligand. In this case, two lithiated intermediates (–)-**3**•(*R*)-**17Li** and (–)-**3**•(*S*)-**17Li** were observed in an almost equimolar quantity (dr: 55:45) and the same chemical shift correlations were verified (Figure 3). The aromatic region of the ^{1}H- and ^{13}C-NMR spectra revealed a double set of signals, one for each diastereomeric complex (–)-**3**•(*R*)-**17Li** and (–)-**3**•(*S*)-**17Li** (Figure 3). Trapping the lithiated intermediates with deuterium source furnished **17-D** as a racemic mixture.

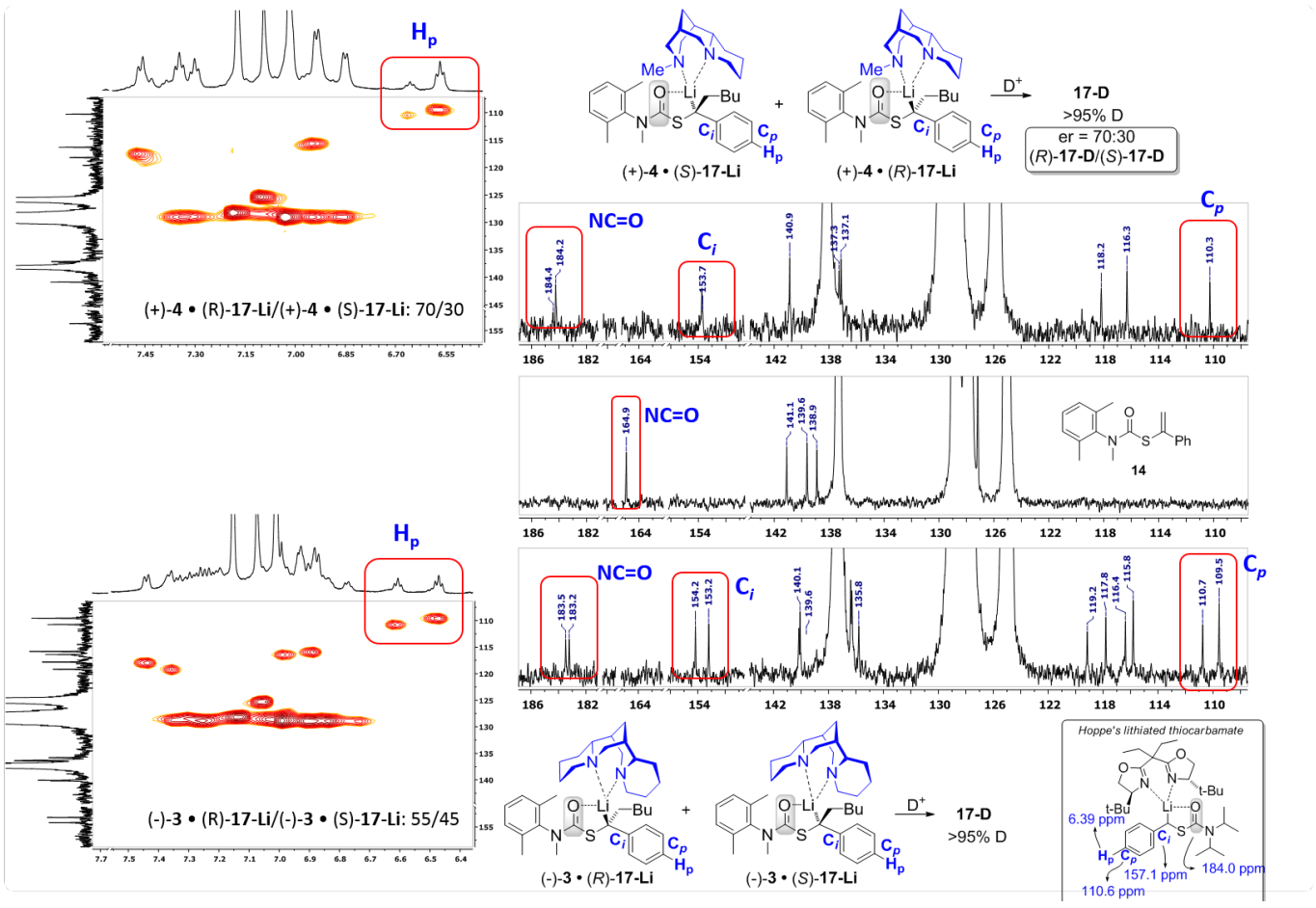
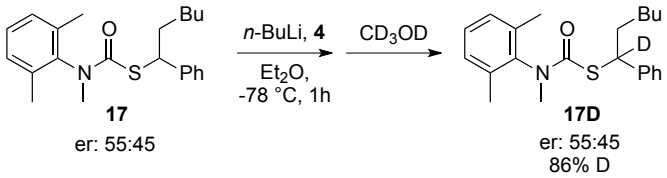


Figure 3. 600 MHz HSQC-DEPT and ^{13}C NMR spectra in toluene-d_8 at 200K for diastereomeric lithiated carbamates (+)-**4**•(*S*)-**17Li** and (+)-**4**•(*R*)-**17Li** (upper part) (–)-**3**•(*S*)-**17Li** and (–)-**3**•(*R*)-**17Li** (lower part). The ^{13}C NMR spectrum of neutral **14** is included as reference.

The identification by NMR of two diastereomeric organolithium complexes confirm that stereoselectivity in the carbolithiation reaction of **14** originates from the diastereoisomeric ratio of organolithiums. In these reactions, it is evident that (+)-sparteine surrogate **4** provides better enantioselectivity than (–)-sparteine **3**. However, these NMR results do not distinguish face selectivity in the addition step from thermodynamically-controlled resolution of the lithiated intermediate.

A simple experiment (Scheme 6) demonstrated that the complex of **17**-Li and **4** is macroscopically configurationally stable at –78 °C. A nearly racemic mixture of **17** was deprotonated using the complex of **4** and *n*-BuLi, to give a mixture of (+)-**4**•(*R*)-**17-Li** and (+)-**4**•(*S*)-**17-Li**, and allowed to equilibrate for an hour. Configurational instability would lead to the same ratio of products as carbolithiation of **14**. However, deuteration of this mixture after 1 h at –78 °C returned **17-D** in the same enantiomeric ratio as the starting **17** (Scheme 6) instead of the 70:30 obtained by carbolithiation of **14** (Table 4, entry 9).



17
er: 55:45

17D
er: 55:45
86% D

Scheme 6. Configurational stability in **17-Li**

Changes in product ratio with time show that our earlier results with **6** and **12** clearly involve configurationally unstable intermediates, so attempts were made to equilibrate the mixtures of (+)-**4**•(*R*)-**17Li** / (+)-**4**•(*S*)-**17Li** and (-)-**3**•(*R*)-**17Li** / (-)-**3**•(*S*)-**17Li** with a warm-cool protocol. If the epimerization occurs, a change of the signal intensities would be expected: such a change was not evident. Warming the 70:30 diastereomeric mixture of (+)-**4**•(*R*)-**17Li** and (+)-**4**•(*S*)-**17Li** in the range 200K → 253K gave only line broadening without changing of the initial diastereomeric ratio. The mixture was kept at 253K for 3h before re-cooling the sample. Temperatures above 253K resulted in decomposition. Similar results were obtained from warm-cool procedures with the 55:45 diastereomeric mixtures of (-)-**3**•(*R*)-**17Li** /(-)-**3**•(*S*)-**17Li**. Only line broadening and a temperature dependent drift were noticed: the signal ratio remained unchanged. The lithiated intermediates were found to be chemically stable for 2 hours at 273K but decomposition occurred at 298K (Figure 4).

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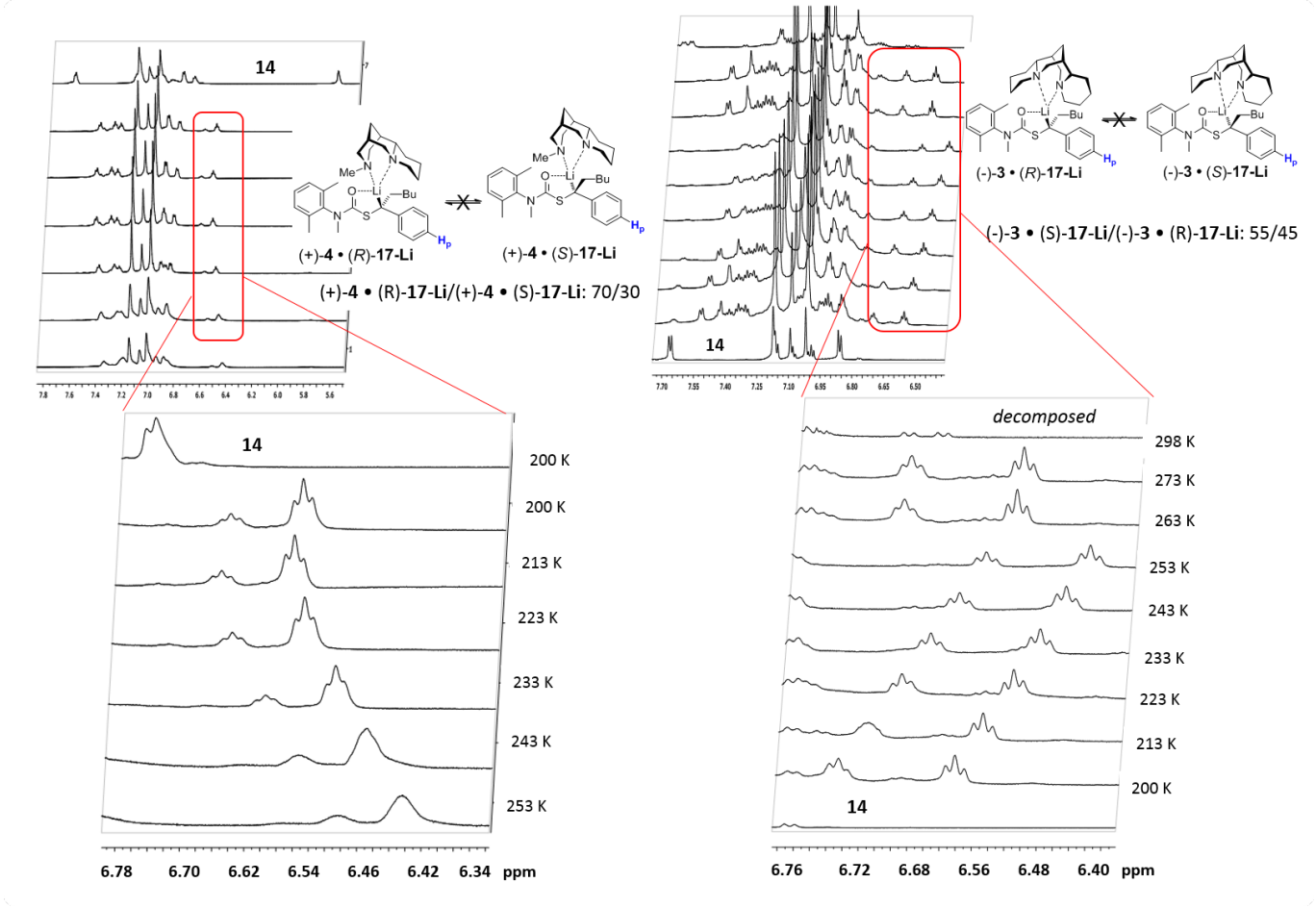

Figure 4. 600 MHz ^{1}H NMR spectra in toluene-d_8 of diastereomeric mixtures of (+)-**4**•(R)-**17-Li** and (+)-**4**•(S)-**17-Li** (left) and (-)-**3**•(R)-**17-Li** and (-)-**3**•(S)-**17-Li** (right). Attempts to demonstrate dynamic thermodynamic resolution.

We thus propose that the lithiated thiocarbamate **17Li** is configurationally stable and that in this case it is likely the stereoselectivity is determined by kinetic control in the addition step with **3**, with **3** and LiCl, or with **4**. Other examples of lithiated α-thio carbanions that are configurationally stable on time scales of minutes to hours have been reported [8] and it seems that the configurational stability in **17Li** arises from presence of bulky substituents at the chiral centre, leading to an enhanced barrier to epimerization relative to **6Li** and **12Li**.

Conclusions

Carbolithiation of alkenylthiocarbamates in the presence of chiral diamine ligands followed by protonation gives enantiomerically enriched products. In some cases, the same enantiomer of the product is obtained whether (–)-sparteine or (+)-surrogate is used, though enantiomeric outcomes in those cases are generally restored by adding LiCl to the reactions of (–)-sparteine. Time-course experiments suggest that the moderate enantioselectivity with (–)-sparteine results from kinetically controlled carbolithiation to give organolithiums that are configurationally stable. NMR experiments confirmed that the enantiomeric ratio in the product reliably corresponds to the observable ratio of diatereoisomeric organolithium complexes in solution, proving that protonation is stereospecific. For some, but not all, lithiated thiocarbamates, the use of (+)-**4** in place of (–)-**3**, or adding LiCl to (–)-**3**, promotes equilibration to give a new, thermodynamically-controlled ratio of products. An N-aryl carbamate **5**, on carbolithiation in THF in the presence of (+)-**4**, led to a tandem enantioselective carbolithiation-rearrangement, generating the thiocarbamate derivative of a tertiary thiol in 63:37 er.

Experimental section

General Methods

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Ultrashield 300, 400, 500 or 600 MHz spectrometer. ^{1}H and ^{13}C spectra were referenced relative to the solvent residual peaks and chemical shifts (δ) reported in ppm downfield of trimethylsilane ($CDCl_3$ δ H: 7.26 ppm, δ C: 77.0 ppm; CD_3OD δ H: 3.31 ppm, δ C 49.05 ppm). Coupling constants (J) are reported in Hertz and rounded to 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or some combination of these. Low and high resolution mass spectra were recorded by staff at the University of Manchester. Electrospray (ES) spectra were recorded on a Waters Platform II and high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP and are accurate to ± 0.001 Da. Infrared spectra were recorded on an Ati Mason Genesis Series FTIR spectrometer as thin films on a sodium chloride plate. Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram. Sil G/UV254) and visualized with UV light at 254 nm; K_2MnO_4 or phosphomolybdic acid dips were used to reveal the products. Flash column chromatography was carried out using Fluorochem Davisil 40-63u 60Å. All reactions were conducted under a nitrogen atmosphere in oven-dried glassware unless stated otherwise. Tetrahydrofuran was distilled under nitrogen from sodium using a benzophenone indicator. Dichloromethane, toluene and diethyl ether were obtained by distillation over calcium hydride under a nitrogen atmosphere. Anhydrous dimethylformamide were purchased from Sigma-Aldrich. Acetonitrile was further dried over 4 Å oven-activated molecular sieves for 1h prior to use. Triethylamine was distilled over calcium hydride under nitrogen atmosphere. Petrol refers to the fraction of light petroleum ether boiling between 40 and 65 °C. All other solvents and commercially available reagents were used as received.

Thiocarbamates **5** and **14** were synthesised as previously described.[20] Carbamoyl chlorides were prepared as previously reported.[42]

***S*-(2-Hydroxy-1-phenylethyl)-*N*-isopropyl-*N*-phenyl thiocarbamate 9**

Thiocarbamate **8**, made by the method of Hoppe,[8] (1.52 mmol) was dissolved in dry THF (20 mL) and added with $LiAlH_4$ (7.6 mmol, 1M solution in Et_2O). The resulting mixture was refluxed overnight, cooled at 0 °C, diluted with AcOEt and quenched by slow addition of HCl 1N. The organic layer was then separated and the aqueous layer was extracted with AcOEt (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude hydroxythiol that was purified by column chromatography using Petroleum ether/AcOEt 4:1 as eluent. **Yield** 75%. **^{1}H NMR** (300 MHz $CDCl_3$) δ 7.23-7.12 (m, 5H), 3.93 (dd, 1H, *J* = 13.9, 6.4 Hz), 3.77-3.71 (m, 1H), 3.65-3.59 (m, 1H), 2.68 (br s, 1H), 1.89 (d, 1H, 6.6 Hz) ppm. **^{13}C NMR** (75 MHz $CDCl_3$) δ 140.6, 128.8, 127.8, 127.5, 68.2, 46.2 ppm. **LRMS** *m/z* (ES+) m/z: 177 $[M+Na]^+$

A solution of this material (1 mmol) in anhydrous THF (8.0 mL) was added dropwise to an ice-cooled suspension of sodium hydride (1.2 mmol, 60% in mineral oil) in THF (30 mL). After 30 min. a solution of *N*-isopropyl-*N*-phenylcarbamoyl chloride[42] in 2 mL of THF was added and the resulting mixture was stirred for 3h at room temperature. The reaction mixture was poured into a mixture of Et_2O and 2M aqueous HCl (30 mL). The organic layer was separated and the aqueous solution was extracted with Et_2O (30 mL). The combined extracts were stirred over solid $Na_2SO_4/NaHCO_3$. The crude product was purified by flash chromatography on silica gel (Et_2O/hexanes, 1:4) to give the product **9** (280 mg, 89%) as an oil. **^{1}H NMR** (300 MHz DMSO-d6) δ 7.44 (m, 3H), 7.28-7.19 (m, 7H), 4.71 (sept, 1H, *J* = 6.7 Hz), 4.46 (t, 1H, *J* = 7.7 Hz), 3.72-3.60 (m, 2H), 1.03 (d, 3H, *J* = 6.7 Hz), 0.98 (d, 3H, *J* = 6.7 Hz) ppm. **^{13}C NMR** (75 MHz DMSO-d6) δ 166.0, 140.3, 136.0, 131.5, 129.0, 128.2, 128.1, 126.8, 64.3, 51.0, 48.1, 20.8, 20.7 ppm. **LRMS** *m/z* (ESI) m/z: 316 $[M+H]^+$.

***S*-(2-trifluoromethanesulphonyloxy-1-phenylethyl)-*N*-isopropyl-*N*-phenyl thiocarbamate 10**

The alcohol **9** (0.37 mmol) was dissolved in dry DCM (10 mL). The solution was cooled at 0 °C and Et_3N (2 mmol), MsCl (0.48 mmol) and DMAP (0.037 mmol) were then added. The resulting mixture was stirred at room temperature overnight. The reaction was diluted with DCM and water (40 mL) was then added. The organic layer was then separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (10 mL) dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude product that was purified by column chromatography using Petroleum ether/AcOEt 3:1 as eluent. The title compound **10** was obtained in quantitative yield. **^{1}H NMR** (300 MHz $CDCl_3$) δ 7.35 (m, 3H), 7.19 (m, 7H), 4.88-4.84 (m, 1H), 4.81-4.76 (m, 1H), 4.59-4.54 (m, 1H), 4.48-4.41 (m, 1H), 2.74 (s, 3H), 1.05 (dd, 6H, *J* = 6.4 Hz) ppm. **^{13}C NMR** (75 MHz $CDCl_3$) δ 166.0, 136.8, 135.8, 131.6, 129.4, 129.1, 128.7, 128.3, 128.0, 71.6, 49.0, 47.8, 37.2, 21.0 ppm. **LRMS** *m/z* (ESI) m/z: 394 $[M+H]^+$.

***S*-(1-Phenylethenyl)-*N*-isopropyl-*N*-phenyl thiocarbamate 11**

Mesylate **10** (0.37 mmol) was dissolved in dry DMF (5 mL) and the solution was cooled at 0 °C. NaH (0.55 mmol) was added and the resulting mixture was stirred at room temperature for 1h. The reaction was diluted with AcOEt and quenched with water. The organic layer was then separated and the aqueous layer was extracted with AcOEt (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude product that was purified by column chromatography using Petroleum ether/AcOEt 4:1 as eluent. **^{1}H NMR** (300 MHz $CDCl_3$) δ 7.65-7.63 (m, 2H), 7.46 (m, 3H), 7.37-7.27 (m, 5H), 5.98 (s, 1H), 5.72 (s, 1H), 4.82 (sept, 1H, *J* = 6.7 Hz), 1.08 (d, 6H, *J* = 6.7 Hz) ppm. **^{13}C NMR** (75 MHz

$CDCl_3$) δ 166.1, 140.2, 139.7, 136.7, 131.6, 129.3, 129.2, 128.2, 128.1, 126.6, 125.1, 48.7, 21.1 ppm. **IR** ν_{max} (film)/cm^{-1} 2974, 1665, 1492, 1238, 1221, 1114. **LRMS** *m/z* (ES+) m/z: 298 $[M+H]^+$, 320 $[M+Na]^+$.

General procedures for the asymmetric carbolithiation of alkenyl thiocarbamates

METHOD A. ASYMMETRIC CARBOLITHIATION

(–)-Sparteine or the (+)-sparteine surrogate[33] (0.14 mmol) was dissolved in dry Et_2O (0.4 mL) and cooled to –78 °C. BuLi (0.11 mmol, 1.6 M solution in hexanes) was added and the resulting mixture was stirred for 20 minutes at 0 °C. In parallel, a solution of the thiocarbamate **5**, **11** or **14** (0.056 mmol) in Et_2O (0.2 mL) was prepared and cooled at -78 °C (if required LiCl (0.5 mmol) was added). The complex sparteine/BuLi was then added at this second solution at -78 °C and the resulting mixture was stirred at the same temparture for the required time. The reaction was then quenched with MeOH and diluted with AcOEt and water. The organic layer was then separated and the aqueous layer was extracted with AcOEt (2 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude product that was purified by column chromatography using hexanes/AcOEt 4:1 as eluent.

METHOD B. ASYMMETRIC CARBOLITHIATION–ARYL MIGRATION

(+)-Sparteine surrogate (0.13 mmol) was dissolved in dry THF (0.4 mL) and cooled to -78 °C. BuLi (0.12 mmol, 1.6 M solution in hexanes) was added and the resulting mixture was stirred for 20 minutes at -78 °C. In parallel, a solution of the appropriate thiocarbamate (0.06 mmol) in THF (0.2 mL) was prepared and cooled at -78 °C. The sparteine surrogate–BuLi complex was then added to this second solution at -78 °C and the resulting mixture was stirred at the same temparture for 1.5h. The reaction was quenched with EtCOOH (0.36 mmol) and diluted with AcOEt and water. The organic layer was then separated and the aqueous layer was extracted with AcOEt (2 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a crude product that was purified by column chromatography using hexanes/AcOEt 4:1 as eluent.

***S*-(1-Phenylhexyl)-*N*-methyl-*N*-4-chlorophenyl thiocarbamate 6**

By method A, using the conditions shown in Table 1, thiocarbamate **5** gave the title compound as an oil **^{1}H NMR** (300 MHz $CDCl_3$) δ 7.29-7.08 (m, 9H), 4.42 (dd, 1H, *J* = 8.9, 6.7 Hz), 3.19 (s, 3H), 1.84-1.76 (m, 2H), 1.21-1.16 (m, 6H), 0.84 (t, 3H, *J* = 6.4, 3H) ppm. **^{13}C NMR** (75 MHz $CDCl_3$) δ 168.2, 142.7, 142.3, 129.3, 128.3, 128.0, 127.0, 126.5, 38.7, 38.4, 33.9, 29.2, 22.6, 17.3, 14.1 ppm. MS (ESI) m/z: 362 $[M+H]^+$. **IR** ν_{max} (film)/cm^{-1} 2954, 2929, 2857, 1657, 1489. **LRMS** *m/z* (ES+) m/z: 384 $[M+Na]^+$, **HRMS** (ESI): calcd for $C_{20}H_{24}NOSClNa$ (M + Na^+) 384.1160, found 384.1163.

***S*-(1-Phenylhexyl)-*N*-isopropyl-*N*-4-chlorophenyl thiocarbamate 12**

By method A, using the conditions shown in Table 2, thiocarbamate **5** gave the title compound as an oil **^{1}H NMR** (300 MHz $CDCl_3$) δ 7.31-7.07 (m, 10H), 4.80 (sept, 1H, *J* = 6.7 Hz), 4.4 (dd, 1H, *J* = 9.2, 6.4 Hz), 1.84-1.68 (m, 2H), 1.18-1.14 (m, 5H), 1.02 (d, 3H, *J* = 6.7 Hz), 0.96 (d, 3H, *J* = 6.7 Hz), 0.74 (m, 4H) ppm. **^{13}C NMR** (75 MHz $CDCl_3$) δ 168.0, 142.7, 136.6, 131.7, 128.9, 128.3, 127.8, 126.7, 125.2, 49.8, 48.4, 37.0, 31.4, 27.3, 22.4, 21.1, 14.0 ppm. **IR** ν_{max} (film)/cm^{-1} 2931, 1649, 1493, 1450, 1279, 1240, 1115, 755. **LRMS** *m/z* (ES+) m/z: 378 $[M+Na]^+$, **HRMS** (ESI): calcd for $C_{22}H_{29}NOSNa$ (M + Na^+) 378.1863, found 378.1865.

***S*-(1-Phenylhexyl)-*N*-methyl-*N*-2,6-dimethylphenyl thiocarbamate 17**

By method A, using the conditions shown in Table 4, thiocarbamate **14** gave the title compound as an oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 0.75 (br. t., 3 H), 1.10 – 1.20 (m, 4 H), 1.60 – 1.80 (m, 2 H), 1.97 (s, 3 H), 2.19 (s, 3 H), 3.07 (s, 3 H), 4.41 (t, *J* = 6.5 Hz, 1 H), 7.05 – 7.20 (m, 8 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 13.0, 16.5, 16.6, 21.4, 26.2, 28.5, 30.4, 34.1, 35.6, 48.5, 125.7, 126.8, 127.2, 127.7, 127.7, 127.8, 136.2, 141.8, 167.4. **IR** ν_{max} (film)/cm^{-1} 2925, 1655, 1647, 1376, 1275, 1084, 867, 696. **LRMS** *m/z* (ES+) m/z: 356 $[M+H]^+$, **HRMS (ESI):** calcd for $C_{22}H_{30}ONS$ [M+H] 356.2048, found 356.2043. A sample of 70:30 er *R*:*S* had $[\alpha]_D$ +20 (*c* = 1, $CHCl_3$).

***S*-Benzyl-*N*-methyl-*N*-2,6-dimethylphenyl thiocarbamate 16**

A solution of benzyl thiol (1 mmol) in anhydrous THF (8.0 mL) was added dropwise to an ice-cooled suspension of sodium hydride (1.2 mmol, 60% in mineral oil) in THF (30 mL). After 30 min. a solution of *N*-methyl-*N*-2,6-dimethylphenylcarbamoyl chloride[42] in 2 mL of THF was added and the resulting mixture was stirred for 3h at room temperature. The reaction mixture was poured into a mixture of Et_2O and 2M aqueous HCl (30 mL). The organic layer was separated and the aqueous solution was extracted with Et_2O (30 mL). The combined extracts were stirred over solid Na_2SO_4/$NaHCO_3$. The crude product was purified by flash chromatography on silica gel (Et_2O/hexanes, 1:4). **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 2.11 (s, 6 H), 3.12 (s, 3 H), 3.99 (s, 2 H), 6.98-7.20 (m, 8 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 17.7, 35.1, 35.4, 127.0, 128.4, 128.9, 129.0, 137.4, 138.5, 138.7, 168.6. **LRMS** *m/z* (ES+) m/z: 286 $[M+H]^+$.

Preparation of alkenyl thiocarbamate 14 using $ClCH_2I$

A solution of *sec*-BuLi (6 mmol of a 1.4 M solution in hexane) was added dropwise to a solution of thiocarbamate **16** (3 mmol) in 25 mL of dry THF -98 °C. The yellowish solution was stirred for 1h at a temperature between -98 – -78 °C. The solution was cooled to -98 °C and a solution of $ClCH_2I$ (6 mmol in 1 mL of dry THF) was added. The resulting mixture was stirred overnight and gradually warmed to room temperature. The reaction was quenched with water and extracted with AcOEt.

The organic extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexanes:AcOEt (85:15) as eluent to yield the title compound **14** (775 mg, 87%) as an oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 2.35 (s, 6 H), 3.16 (s, 3 H), 5.74 (s, 1 H), 6.00 (s, 1 H), 7.20 – 7.40 (m, 6 H), 7.60 – 7.70 (m, 2 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 17.7, 35.4, 125.5, 126.8, 128.1, 128.2, 129.0, 129.2, 137.5, 138.9, 139.0, 140.5, 166.9. **IR** ν_{max} (film)/cm^{-1} 2922, 1670, 1489, 1336, 1084, 862, 769. **LRMS** *m/z* (ES+) m/z: 298 $[M+H]^+$, **HRMS (ESI):** calcd for $C_{18}H_{20}ONS$ [M+H] 298.1266, found 298.1268.

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Electronic Supplementary Information (ESI) available: detailes of NMR and IR experiments. Full characterisation data for new compounds. Details of stereochemical assignments. See DOI: 10.1039/b000000x/

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