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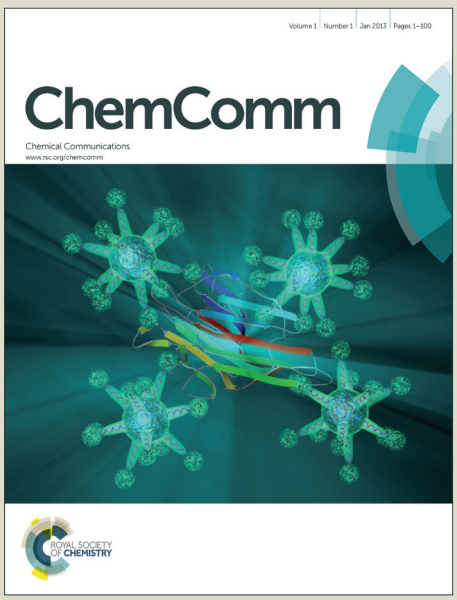

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Dihydrothiophenes containing quaternary stereogenic centres by sequential stereospecific rearrangements and ring-closing metathesis

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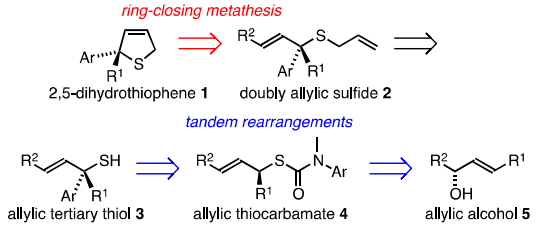
Stereospecific [3,3]-sigmatropic rearrangement of *O*-substituted thiocarbamate derivatives of enantiopure allylic alcohols provides allylic thiocarbamates as single enantiomers. Intramolecular arylation by rearrangement of their allyllithium derivatives provides allylic tertiary thiols. Allylation and ring-closing metathesis gives 2,5-dihydrothiophenes containing sulfur-bearing quaternary centres.

Dihydrothiophenes and tetrahydrothiophenes are important motifs in the context of natural products, biologically active compounds, and materials chemistry.[1] Nevertheless, their stereoselective synthesis has received little attention.[1a,b] Earlier diastereoselective methods[1d-f] were recently enhanced by the report from Xu and co-workers of an enantioselective synthesis of 2,5-dihydrothiophene-3-carbaldehydes by domino thia-Michael/aldol condensation reactions.[1c,2] Dihydrothiophenes containing a quaternary chiral center provide a motif of particular interest for pharmaceutical applications[3] which occurs in the thiotetronic acid antibiotics[3a-c] including (*R*)-thiolactomycin,[3b,4] and in dideoxyspirothio nucleoside analogues with antiviral and anticancer properties.[3d]

In this paper we report the construction of enantiomerically enriched 2,5-dihydrothiophenes **1** by ring-closing metathesis of doubly allylic sulfides[5] **2** derived from tertiary thiols **3** (Scheme 1), themselves made from readily-obtained chiral allylic alcohols by a pair of tandem stereospecific rearrangements.

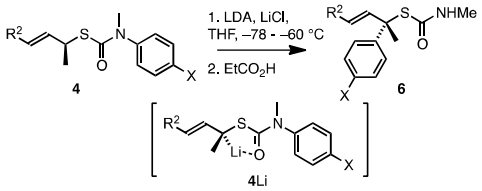


Scheme 1: Dihydrothiophenes from allylic alcohols.

The synthesis of five- and six-membered heterocycles by ring-closing metathesis is well established,[6,7] but for the synthesis of sulfur heterocycles its use is rare and reportedly problematic.[5,8] Nonetheless, coordination to sulfur has been proposed to enhance Ru-promoted cross-metathesis of allyl sulfides.[9]

We have previously shown[10] that certain allylic thiols **3** required as precursors for such an approach may be made by rearrangement of the anionic derivatives of a class of allylic thiocarbamates, but that the stereospecificity of the rearrangement (which involves N to C migration of an aryl or vinyl group) was typically compromised by the incomplete configurational instability of the allyllithium intermediate.

Reasoning that dipole-stabilised[11] allyllithiums bearing γ-substituents typically should show greater configurational stability than those substituted only at the α-position,[12] we explored the possibility of using the migration of an aryl ring from N to C within substituted thiocarbamates **4** as a means of obtaining tertiary allylic thiols **3** with reliable stereospecificity. Three pairs of allylic thiocarbamates **4** bearing π electron-donating groups (Scheme 2) were deprotonated with LDA in order to compare the behaviour of the substituted and unsubstituted series, and the results are shown in Table 1.



Scheme 2: Stereospecificity in the rearrangement of allylic thiocarbamates.

Table 1: The effect of a γ-substituent on the stereospecificity of the arylation of allylic thiocarbamates.

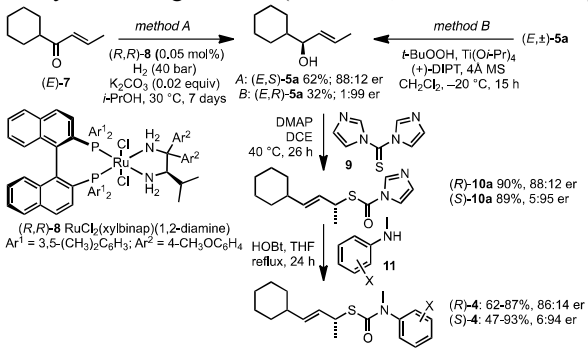
	R^2 = H			R^2 = cyclohexyl		
X	SM	**6**, yield	er	SM	**6**, yield	er
MeO	**4a**	0	–	**4d**	**6d**, 24	–
Me	**4b**[a]	**6b**, 11	57:43	**4e**	**6e**, 76	91:9
F	**4c**[a]	**6c**, 40	70:30	**4f**	**6f**, 82	94:6

[a]Data from ref. 10a.

It is evident that the more substituted allyllithium intermediates **4d**Li-**4f**Li rearrange in higher yield and with higher stereospecificity—almost complete in the formation of

6e and **6f**. Only the *p*-OMe-substituted thiocarbamate **4d** still failed to rearrange efficiently in the more substituted case. **4a** failed to rearrange, but NMR of the reaction mixture showed that the intermediate organolithium **4a**Li was nonetheless formed,[13] indicating that the poor performance of **4a-4c** was indeed due to the slow migration of the aryl ring to the less substituted, and therefore less reactive, allyllithium.

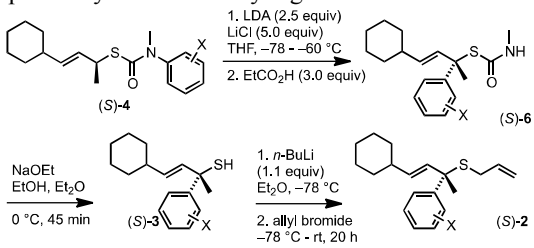
Substituted thiocarbamates **4** may be synthesised by stereospecific [3,3]-sigmatropic rearrangement of enantiopure allylic alcohols **5**.[14] Given that the terminal substituent R^2 is lost in the final metathesis step leading to **1**, we elected to start with the readily accessible cyclohexyl-substituted substrates **5a** and **7**. Ketone **7** was reduced enantioselectively to the allylic alcohol (*S*)-**5a** using Noyori's catalyst **8**,[15] and (±)-**5a** underwent Sharpless kinetic resolution to leave behind (*R*)-**5a** in lower yield but higher e.r.[16] (Scheme 3, Methods A and B).



Scheme 3: Synthesis of enantiomerically enriched thiocarbamates **4** by stereospecific *in situ* [3,3]-sigmatropic rearrangement.

Treatment of either (*S*)- or (*R*)-**5a** with thiocarbonyldiimidazole **9** formed imidazole derivatives **10** directly by acylation of the allylic alcohol and *in situ* [3,3]-sigmatropic rearrangement of the resulting *O*-allylthiocarboxylimidazole species.[17] This rearrangement was fully enantiospecific, and nucleophilic displacement of the imidazole group in **10** with *N*-methylanilines[17] **11** gave a series of *S*-allylthiocarbamates **4** in enantiomerically enriched form (Scheme 3 and Table 2).

The thiocarbamates **4** were treated with LDA at –78 °C in order to form their allyllithium derivatives, which on warming to –60 °C underwent intramolecular *N* to *C* aryl migration to yield the tertiary thiocarbamates **6** (Table 2). Quenching the anionic products with propionic acid at low temperature prior to work-up avoided partial hydrolysis of the products. Rearranged products were obtained with both electron-rich and electron-deficient migrating rings, and in contrast with the rearrangements of less substituted allyllithiums[10] stereospecificity was uniformly high.



Scheme 4: Stereospecific aryl migration in cyclohexyl-substituted allylic thiocarbamates **4**

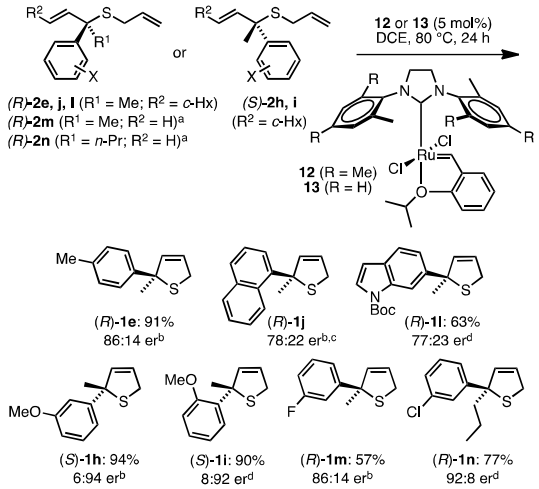
Table 2: Synthesis of enantioenriched allylsulfides by stereospecific aryl migration

entry	X	**4** (er, *S*:*R*)	**6**, yield (er, *S*:*R*)	**3**, yield	**2**, yield
1	4-Me	(*S*)-**4e** (94:6)	(*S*)-**6e**, 76 (91:9)	–	–
2	4-Me	(*R*)-**4e** (13:87)	(*R*)-**6e**, 100 (13:87)	(*R*)-**3e**, 91	(*R*)-**2e**, 76
3	4-F	(*S*)-**4f** (94:6)	(*S*)-**6f**, 82 (94:6)	(*S*)-**3f**, 56	–
4	4-Cl	(*S*)-**4g** (95:5)	(*S*)-**6g**, 63 (94:6)[a]	**3g**,[b] 56	–
5	3-OMe	(*S*)-**4h** (95:5)	(*S*)-**6h**, 100 (95:5)	(*S*)-**3h**, 72	(*S*)-**2h**, 100
6	2-OMe	(*S*)-**4i** (94:6)	(*S*)-**6i**, 100 (94:6)	(*S*)-**3i**, 61	(*S*)-**2i**, 98
7	2,3-benzo [Ar = 1-naphthyl]	(*R*)-**4j** (14:86)	(*R*)-**6j**, 71 (15:85)	(*R*)-**3j**, 90	(*R*)-**2j**, –[c]
8	– [Ar = 2-pyridyl]	(*S*)-**4k** (94:6)	(*S*)-**6k**, 30 (93:7)	–	–
9	*N*-Boc-3,4-pyrrolo [Ar = *N*-Boc-6-indolyl]	(*S*)-**4l** (95:5)	(*S*)-**6l**, 41 (90:10)	**3l**,[b,d] 58	**2l**,[b] 53

[a]At –50 °C. [b]Using racemic material. [c]Inseparable from by-product **2j'**: see supporting information. [d](*R*)-**3l** was obtained in 39% yield from (*R*)-**6l**.

Basic hydrolysis of thiocarbamates **6** revealed tertiary thiols **3**, which were *S*-allylated under standard conditions to yield the sulfides **2** (Scheme 4 and Table 2). Despite the presence of the sulfur atom and the adjacent quaternary centre, the allyl sulfides **2** underwent ring-closing metathesis[5] to dihydrothiophenes **1** in the presence of **12**[5,18a] or **13**[18b] in 63-94% yield (Scheme 5).

The absolute configuration of the dihydrothiophenes **1** was confirmed by comparison of experimental and calculated circular dichroism (CD) spectra of (*R*)-**1e**. The geometry of (*R*)-**1e** was optimised at the B3LYP/6-311G(d,p) level and electronic CD spectra were generated, within the time-dependent density functional formalism, for conformations at 10° intervals about the aryl-thiophene bond.[19] These spectra were Boltzmann weighted according to the potential energy of the conformation to give the calculated CD spectrum shown along with the experimental spectrum of (*R*)-**1e** in methanol in Figure 1. The matching form of the spectra leads us to assign *R* configuration to the stereogenic centre of (*R*)-**1e**.



Scheme 5: Ring-closing metathesis of allylsulfides **2** to yield dihydrothiophenes **1**. [a]Prepared by the method of ref. 10a. [b]Using catalyst **12**. [c]Yield not determined as the starting material contained an impurity. [d]Using catalyst **13**.

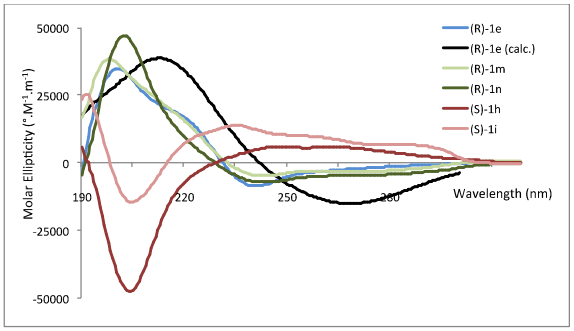


Figure 1 Experimental and electronic CD spectra of (*R*)-**1e** and experimental CD spectra of (*R*)- and (*S*)-2,5-dihydrothiohenes **1**.

The CD spectra of (*R*)-**1m** and (*R*)-**1n** took a similar form to that of (*R*)-**1e**, while those of (*S*)-**1h** and (*S*)-**1i** were inverted. These results (in conjunction with the established suprafacial stereospecificity of the [3,3]-sigmatropic rearrangement giving **10**) confirm that the migration of the aryl ring proceeds with retention of absolute configuration, as observed in related benzylic thiocarbamates.[20]

In summary, enantiomerically enriched dihydrothiophenes may be synthesised from enantiomerically enriched allylic alcohols by intramolecular arylation of their allylic thiocarbamate derivatives followed by ring closing metathesis. The work expands the scope of heterocyclic synthesis by ring-closing metathesis,[7] allowing the incorporation both of sulfur,[5,8] and of a sterically hindered quaternary stereogenic centre.[18,21]

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† Electronic Supplementary Information (ESI) available: Full experimental details for new compounds. See DOI: 10.1039/c000000x/

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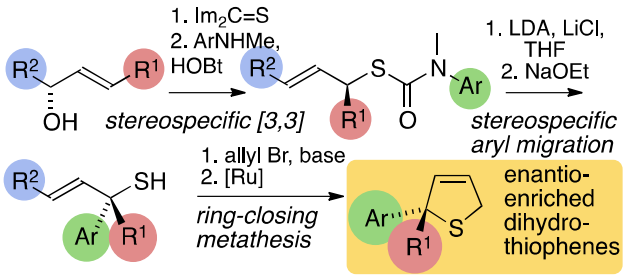
Graphical abstract



Tandem stereospecific rearrangements by [3,3]-sigmatropic shift and N to C aryl migration give tertiary thiols that undergo ring closing metathesis to dihydrothiophenes.