Stereo- and Regio-selective Synthesis of Polyfunctionalized Cyclopropanes

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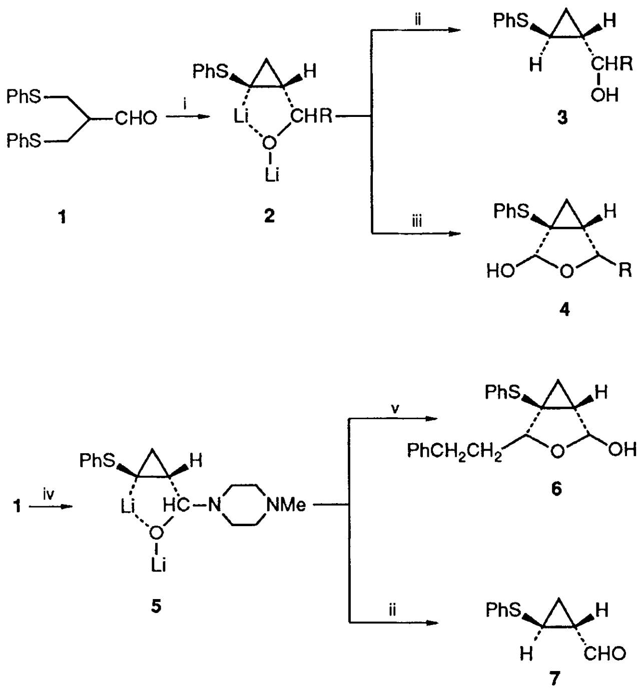
The reaction of 3-phenylthio-2-(phenylthiomethyl)propanal with organolithium reagents and carbonyl compounds provides a stereo- and regio-selective one-pot route to polyfunctionalized cyclopropane derivatives.

Stereo- and regio-selective routes to functionalized cyclopropanes would be of significant value not only because these cyclopropanes are frequently found in naturally occurring compounds such as chrysanthemic acid,[1] dictyopterene[2] and coronatin,[3] but also because they are important intermediates for the construction of more complex molecules like hybridalactone.[4] Bi- and poly-functionalized cyclopropanes in particular are promising intermediates for the versatile elaboration of four-,[5], five-,[6] seven-[7] and eleven-membered rings[8] *via* vinylcyclopropane rearrangement and 1,4-dienes *via* solvolytic rearrangement.[9] We have now found that 3-phenylthio-2-(phenylthiomethyl)propanal **1** provides bi- and poly-functionalized cyclopropanes with high stereo- and regio-selectivities in a one-pot procedure *via* addition of organolithium reagents to **1** followed by cyclopropanation and trapping with electrophiles. The aldehyde **1** can be readily prepared in 94% yield by reduction of methyl 3-phenylthio-2-(phenylthiomethyl)propanoate[10] with diisobutylaluminium hydride in tetrahydrofuran (THF). Reaction of **1** with 1 equiv. of methyllithium in THF at −30 °C for 1 h, followed by treatment with 2 equiv. of butyllithium at −78 °C for 30 min and at 0 °C for 2 h gave the dilithium salt **2**. Quenching the reaction mixture with water produced *trans*-1-(2-phenylthiocyclopropyl)ethanol **3a** in 78%

Table 1 Stereo- and regio-selective synthesis of polyfunctionalized cyclopropanes

Lithium reagent	Electrophile	Product	Yield (%)
MeLi	H_2O	**3a**, R = Me	78
Bu^{n}Li	H_2O	**3b**, R = Bu^n	70
PhLi	H_2O	**3c**, R = Ph	96
MeLi	DMF	**4a**, R = Me	84
Bu^{n}Li	DMF	**4b**, R = Bu^n	72
PhLi	DMF	**4c**, R = Ph	89
PhSC(Li)CH_2CH_2	DMF	**4d**, R = –C(SPh)CH_2CH_2	76
MeN$(CH_2)_2$N(Li)CH_2CH_2	Ph$(CH_2)_2$CHO	**6**	75
MeN$(CH_2)_2$N(Li)CH_2CH_2	H_2O	**7**	73



Scheme 1 *Reagents and conditions*: i, lithium reagent (1 equiv.; see Table 1), BuLi (2 equiv.), THF; ii, H_2O; iii, DMF; iv, 1-lithio-4-methylpiperazine (1 equiv.), BuLi (2 equiv.); v, $Ph(CH_2)_2CHO$

yield and the reaction with dimethylformamide (DMF) at −78 °C gave the bicyclic lactol **4a**. The formation of the lactol indicates that the initial cyclopropanation proceeds stereoselectively to give the *trans*-dilithio species **2**, probably owing to internal chelation,[11] and subsequent introduction of the formyl group provides the *cis*-γ-hydroxy aldehyde, which cyclizes spontaneously upon aqueous work-up. This procedure provides a variety of bi- and poly-functionalized cyclopropanes in good overall yields as shown in Table 1.

Addition of 1-lithio-4-methylpiperazine[12] to **1** and cyclopropanation of the adduct by 2 equiv. of butyllithium produced a yellow solution of the *trans*-dilithium species **5**, which gave a regioisomer of the lactol **4** upon treatment with an electrophile. Thus, the addition of 3-phenylpropanal as the electrophile afforded lactol **6** in 75% overall yield.† The *trans*-geometry of the cyclopropanation was confirmed by isolation in 73% yield of *trans*-2-(phenylthio)cyclopropanecarbaldehyde **7** by quenching the dilithium salt with water.

These one-pot syntheses of bi- and poly-functionalized cyclopropane derivatives are attractive because both regioisomers of lactols can be prepared from the readily available starting material **1** by selecting the organolithium reagent and electrophile, and they serve as versatile building blocks for cyclobutanones and 1,4-dicarbonyl and 1,4-diene systems.[13]

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† To a solution of 1-lithio-4-methylpiperazine (4.2 mmol) in THF (25 ml) was added at −78 °C the aldehyde **1** (3.5 mmol) in THF (5 ml) dropwise. After addition was complete, the mixture was stirred at −78 °C for 15 min before warming to −30 °C for 1 h. The solution was cooled to −78 °C, and butyllithium (7.7 mmol) was added dropwise. The mixture was warmed to 0 °C during 2 h. The solution of the resulting dilithium reagent was recooled to −78 °C and 3-phenylpropanal (7.0 mmol) in THF (5 ml) was added. The mixture was stirred for 30 min and allowed to warm to room temperature. Extractive work-up and chromatographic separation gave the lactol **6** (0.82 g, 75%) as a viscous liquid. Satisfactory elemental analyses were obtained.