

Stereo- and Regio-selective Synthesis of Polyfunctionalized Cyclopropanes

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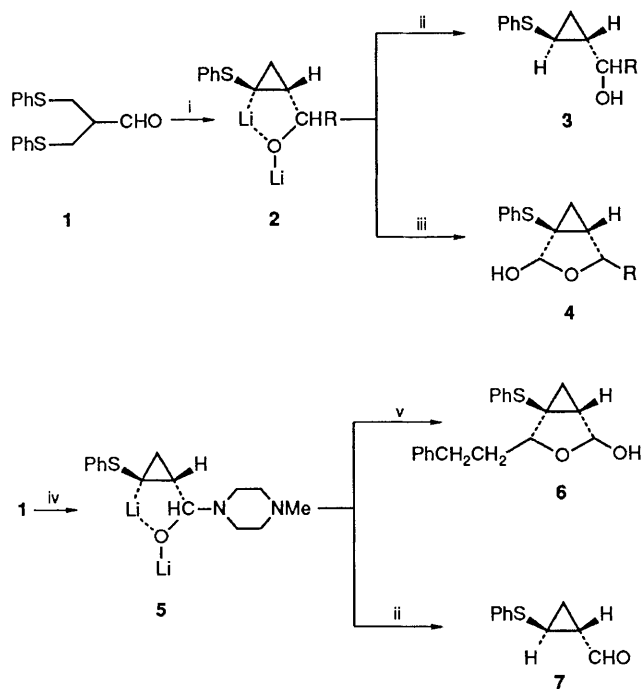
The reaction of 3-phenylthio-2-(phenylthiomethyl)propanal with organolithium reagents and carbonyl compounds provides a stereo- and regio-selective one-pot route to polyfunctionalized cyclopropane derivatives.

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 dictyopterene² and coronatin,³ but also because they are important intermediates for the construction of more complex molecules like hybridolactone.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 rings⁸ 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)propanoate¹⁰ with diisobutylaluminium hydride in tetrahydrofuran (THF). Reaction of **1** with 1 equiv. of methyl lithium in THF at $-30\text{ }^{\circ}\text{C}$ for 1 h, followed by treatment with 2 equiv. of

butyllithium at $-78\text{ }^{\circ}\text{C}$ for 30 min and at $0\text{ }^{\circ}\text{C}$ 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 ₂ O	3a , R = Me	78
Bu ⁿ Li	H ₂ O	3b , R = Bu ⁿ	70
PhLi	H ₂ O	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
PhS $\overline{\text{C}}(\text{Li})\text{CH}_2\text{CH}_2$	DMF	4d , R = $-\overline{\text{C}}(\text{SPh})\text{CH}_2\text{CH}_2$	76
MeN $\overline{(\text{CH}_2)_2\text{N}(\text{Li})\text{CH}_2\text{CH}_2$	Ph(CH ₂) ₂ CHO	6	75
MeN $\overline{(\text{CH}_2)_2\text{N}(\text{Li})\text{CH}_2\text{CH}_2$	H ₂ O	7	73



Scheme 1 Reagents and conditions: i, lithium reagent (1 equiv.; see Table 1), BuLi (2 equiv.), THF; ii, H₂O; iii, DMF; iv, 1-lithio-4-methylpiperazine (1 equiv.), BuLi (2 equiv.); v, Ph(CH₂)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-methylpiperazine¹² 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)cyclopropane-carbaldehyde **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.