A Sulfur-assisted Regioselective α-Functionalization of Cyclopropyl Sulfides. Synthetic Applications of Homoallyl Anion Synthon

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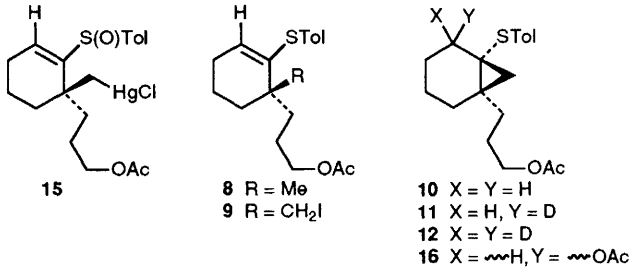
γ,δ-Unsaturated γ-sulfenyl or sulfinylalkylmercury chlorides **5** and **15**, generated from the cyclpropyl sulfide **7** and mercury(II) trifluoroacetate, were demonstrated to be homoallyl anion synthons; these compounds recyclized into the α-functionalized cyclopropyl sulfide on reaction with several electrophiles.

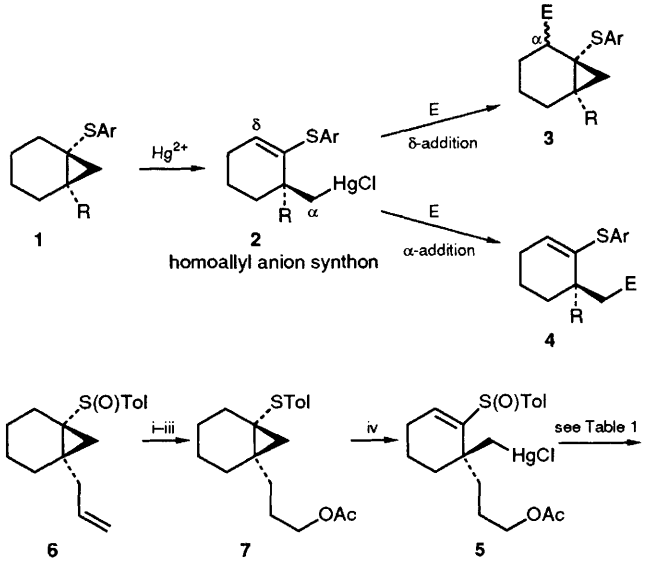
As described in related work,[1] we have found that the regioselective ring-opening reaction of the cyclopropyl sulfide **1** with mercury(II) salts produced γ,δ-unsaturated γ-sulfenylalkylmercury chlorides **2**, homoallyl anion synthons which had two reactive sites at the α- and δ-position, and also demonstrated the spiroannulation reaction utilizing intramolecular α-addition. Thus far, the reaction at the δ-site resulting in cyclopropanation (**2** → **3**) has not been reported in contrast to the substitution reaction at the α-position (**2** → **4**). Furthermore, few methods have been reported for functionalizing methylene groups adjacent to a cyclopropane ring (**1** → **3**), except for nonregioselective oxidation[2] and halogenation,[3] in spite of the versatility of cyclopropyl compounds in synthetic organic chemistry.[4] We now report a novel regioselective δ-functionalisation method (protonation, allylation, acetoxylation *etc.*) of **5** as a model compound for the γ,δ-unsaturated γ-sulfenylalkylmercury chloride **2**.

We started with the preparation of **5** from the chiral cyclopropyl sulfoxide **6**, obtained diastereoselectively as previously described,[1] *via* acetate **7** as outlined in Scheme 1. In order to investigate the reactivity of **5** as a homoallyl anion synthon, we examined various reaction conditions; representative results are summarized in Table 1. The first two examples (runs 1 and 2) in Table 1 illustrate the normal α-site substitution reaction. These results would be expected from previous work. In contrast, other reactions (runs 3–5 and 7) show the novel regioselective δ-site additive reaction accompanied with cyclopropanation. In run 3, conditions for deprotection of the vinylic sulfide to give the ketone ($TiCl_4$, AcOH, 25 °C)[5] converted **5** into the cyclopropyl sulfide **10** quantitatively. To study the reaction mechanism, the same reaction was carried out in deuteriated acetic acid (AcOD) in place of AcOH to yield the dideuteriated product **12** along with a small amount (<8%) of the monodeuteriated product **11** (run 4).† This result suggests the possibility of initial protonation to the vinylic sulfide followed by nucleophilic attack of the hypervalent alkylmercury chloride[6] rather than anion migration from **5** to **5a** followed by proton trapping (Scheme 2).‡

Runs 5–7 demonstrate the utility of this recyclization reaction. Allyl and nitrile groups were introduced at the δ-position by treatment with allyl iodide or chlorosulfonyl isocyanate (CIS)[7] to give **13** and **14** in moderate yields, respectively. Formation of compounds **13** and **14** can be explained by the same mechanism as depicted in Scheme 2. Failure of recyclization in the case of run 6 may be attributed to the decrease in electron density of the vinylic sulfide owing to the substitution of the electron-withdrawing group (*e.g.* nitrile). Moreover, application of the Pummerer rearrangement[8] to the sulfoxide **15**, which was synthesized in 82% yield by *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of **5**, afforded the desired α-acetoxy cyclopropane **16**.

In conclusion, electrophilic addition to **5** and **15** proceeded





Scheme 1 *Reagents and conditions*: i, $(CF_3CO)_2O$, NaI, acetone, 0 °C (100%); ii, $BH_3{\cdot}Me_2S$, tetrahydrofuran (THF), 0 °C; 3 mol dm^{-3} NaOH, 30% H_2O_2 room temp. (84%); iii, Ac_2O, pyridine, room temp. (92%); iv, $Hg(OCOCF_3)_2$, NaOAc, CH_2Cl_2, room temp.; aq. NaCl, CH_2Cl_2, room temp. (84%) (Tol = *p*-tolyl)

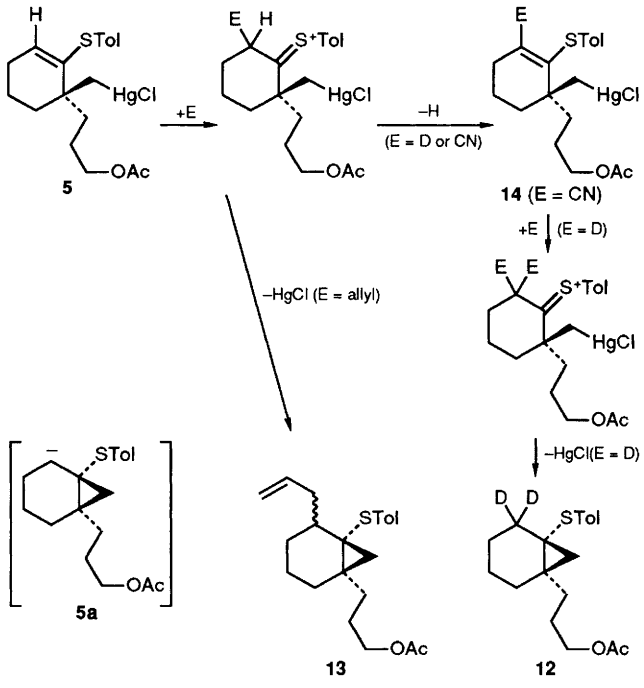
Table 1 α- or δ-functionalization of γ,δ-unsaturated γ-sulfenylalkylmercury chloride with various electrophiles

Run	Substrate	Conditions[a]	Product	Yield (%)[b]
1	**5**	Bu^n_3SnH, CH_2Cl_2, −40 °C	**8**	43[c]
2	**5**	I_2, Bu^n_4NI, CH_2Cl_2	**9**	100
3	**5**	$TiCl_4$, AcOH	**10**	100
4	**5**	$TiCl_4$, AcOD	**11**,**12**	98[d]
5	**5**	$CH_2{=}CHCH_2I$, C_6H_6, reflux	**13**	45
6	**5**	$O{=}C{=}NSO_2Cl$, CH_2Cl_2	**14**	39
7	**15**	Ac_2O, NaOAc, reflux	**16**	41

[a] Room temp. unless otherwise noted. [b] Isolated yields. [c] The dialkylmercury was also isolated along with **8**. [d] Exact distribution of **11** and **12** was not determined.†

† The structures of **11** and **12** were deduced from mass and 200 MHz ^1H NMR spectroscopy. In the mass spectrum, the parent peak of the product shifted from M^+ to $M^+{+}2$ in comparison with **7**. The signals due to the two δ-protons observed at δ 2.0–2.5 in the ^1H NMR spectrum of **6**, were almost absent from the spectra of the products **11** and **12**. From the decrease in integration for the δ-protons, the product **12** was 96% deuteriated.

‡ When **7** was treated with $HgCl_2$ in AcOD or $TiCl_4$ in AcOD, neither **11** nor **12** could be obtained. Although the precise mechanism is not yet clear, the requirement of $HgCl_2$ and $TiCl_4$ for exchange of the δ-protons suggests a cyclopropyl ring-opening intermediate such as a γ-sulfenyl homoallylic anion equivalent.



Scheme 2 Possible mechanism for the formation of δ-functionalized products **12–14**

regioselectively to provide the novel δ-functionalized products **13**, **14** and **16** in moderate yields. In view of their regiospecificity and brevity, these methods should provide access to cyclopropyl compounds which are as yet unknown or are accessible with difficulty.

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References

1 T. Imanishi, T. Ohra, K. Sugiyama, Y. Ueda, Y. Takemoto and C. Iwata, *J. Chem. Soc., Chem. Commun.*, in the press.
2 E. Proksch and A. de Meijere, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 761; T. Hasegawa, H. Niwa and K. Yamada, *Chem. Lett.*, 1985, 1385.
3 P. K. Freeman, T. D. Ziebarth and R. S. Raghavan, *J. Am. Chem. Soc.*, 1975, **97**, 1875; A. de Meijere, O. Schallner, C. Weitemeyer and W. Spielmann, *Chem. Ber.*, 1979, **112**, 908.
4 H. N. C. Wong, M.-Y. Hon, C.-W. Tse and Y.-C. Yip, *Chem. Rev.*, 1989, **89**, 165, references cited therein; A. de Meijere, *Topics in Current Chemistry, Small Ring Compounds in Organic Synthesis I—IV*, vols **133**, **135**, **144**, **155**, Springer-Verlag, Berlin, 1986, 1987, 1988, 1990.
5 D. Seebach and H. Neumann, *Chem. Ber.*, 1974, **107**, 847.
6 G. A. Russell, C.-F. Yao, R. Rajaratnam and B. H. Kim, *J. Am. Chem. Soc.*, 1991, **113**, 373.
7 Introduction of the nitrile group into electron-rich alkenes with CIS has been reported: C. Nativi, G. Palio and M. Taddei, *Tetrahedron Lett.*, 1991, **32**, 1583.
8 T. Matsuda, T. Numata, N. Furukawa and S. Oae, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1302.