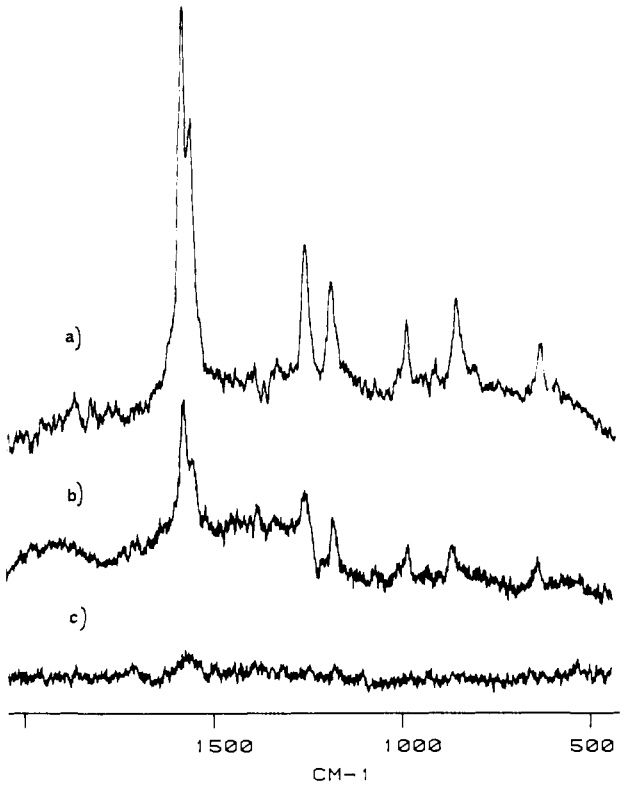


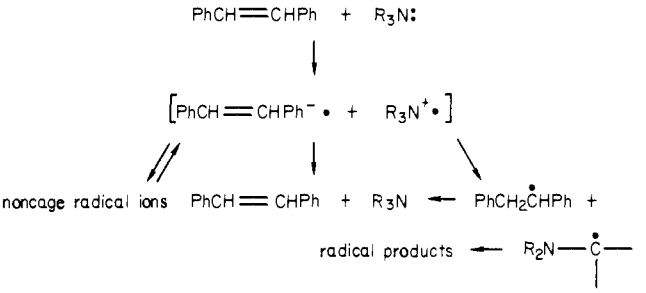
Figure 2. Raman difference spectra of *trans*-stilbene (0.01 M) and ethyldiisopropylamine (1.0 M) in acetonitrile solution at time delays of (a) 100 ns, (b) 500 ns, (c) 2.5 μs.

1577/1553 cm^{-1} peaks in the difference spectra with the intensity of the solvent bands around 1400 cm^{-1} at various time delays. This procedure normalizes the transient intensity for each measurement in the series to equal laser intensity. The data obtained obey a second-order rate law and provide a decay time for the stilbene anion radical Raman signal of ca. 300 ns with both amines. The signal intensity is a function (inter alia) of the radical ion concentration and its resonance Raman scattering cross section. Thus the signal decay time may not equal the anion radical lifetime. We estimate that the quantum yield for stilbene anion radical is ≤0.1, based on the equally good compensation of the bands from *trans*-stilbene and the solvent in the TR[3] spectra.

On the basis of previous chemical investigations, the mechanism of product formation upon reaction of singlet stilbene and tertiary amines (eq 1) was proposed to proceed via initial one-electron transfer to generate a stilbene anion radical–amine cation radical pair followed by proton transfer to yield a free-radical pair.[3] Radical pair combination and disproportionation completes the mechanism for product formation (Scheme I). The observation of the stilbene anion radical by TR[3] spectroscopy provides the first direct evidence for electron-transfer quenching of singlet *trans*-stilbene by tertiary amines. Since geminate (in cage) radical ion pairs are known to react or diffuse apart within several nanoseconds of their formation,[9] the stilbene anion radicals observed in the present investigation must arise from diffusion of the initially formed radical ion pair. Both the observed lifetime and second-order decay of the stilbene anion radical are indicative of homogeneous (out of cage) recombination with an amine cation radical as the exclusive decay pathway for the stilbene anion radical.[10]

The observation of stilbene anion radical formation with both ethyldiisopropylamine and Dabco supports an electron-transfer mechanism for quenching of singlet *trans*-stilbene by both amines.

Scheme I



The absence of stilbene–Dabco adduct formation might be due to the high kinetic stability of the Dabco cation radical or more rapid decay of the radical ion pair for Dabco vs. tertiary monoamines.[11] There are reports that singlet quenching by Dabco results in more rapid nonradiative decay to the ground state and/or intersystem crossing to the triplet state than is the case for quenching by tertiary monoamines.[12] Intersystem crossing of *trans*-stilbene exciplexes is known to yield triplet stilbene which undergoes isomerization to yield *cis*-stilbene.[13] On the basis of the measured quantum yields for *cis*-stilbene formation, intersystem crossing is found to be the predominant decay pathway for the radical ion pairs formed from singlet *trans*-stilbene with either Dabco or ethyldiisopropylamine. Thus rapid nonradiative decay cannot account for the inefficient formation of a stilbene–Dabco adduct. The dynamics of singlet stilbene–amine interactions are under continued investigation in our laboratories.[14]

Registry No. Dabco, 280-57-9; ethyldiisopropylamine, 7087-68-5; *trans*-stilbene, 103-30-0; *trans*-stilbene anion radical, 34473-61-5.

(9) Schulten, K.; Staerk, H.; Weller, A.; Werner, H.-J.; Nickel, B. *Z. Phys. Chem. (Wiesbaden)* **1976**, *101*, 371-382.
(10) Homogeneous radical ion pair recombination should yield both singlet and triplet geminate pairs. The latter may be responsible for the formation of *cis*-stilbene.
(11) Nelsen, S. F. *Isr. J. Chem.* **1979**, *18*, 45-55.
(12) Watkins, A. R. *Aust. J. Chem.* **1980**, *33*, 177-180.
(13) Lewis, F. D.; Simpson, J. T. *J. Phys. Chem.* **1979**, *83*, 2015-2019.
(14) Travel expenses for this project were provided by Nato Research Grant 1911. Support of the work at Northwestern by the National Science Foundation (CHE-8026020) is gratefully acknowledged.

Catalytic Multiple Template-Directed Steroid Chlorinations

Ronald Breslow* and Dennis Heyer

Department of Chemistry, Columbia University
New York, New York 10027
Received November 16, 1981

We have described[1-5] several examples of template-directed chlorinations using the radical-relay mechanism. In this process a chlorinating agent delivers a chlorine atom to a template, which then relays it to the hydrogen atom of an attached substrate. The geometrical relationship between the template atom and the substrate determines which hydrogen is actually attacked. The result of this process is that the template is serving only a catalytic function and is regenerated, so that for instance it can be removed from the product chemically and reisolated. Of course a more interesting process would be one in which the regenerated template were in a position to attack additional substrate molecules, leading to true turnover catalysis. We report a first approximation to this situation, in which a single template is attached to three substrate molecules. As hoped, the reaction with this system indeed functionalizes all three substrates, as the template successively

(1) Breslow, R.; Corcoran, R. J.; Snider, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 6791.
(2) Breslow, R.; Snider, B. B.; Corcoran, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 6792.
(3) Snider, B. B.; Corcoran, R. J.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 6580.
(4) Breslow, R.; Corcoran, R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905.
(5) For a review, see: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

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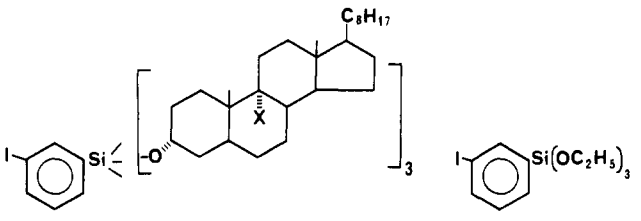
directs attack on one after another. Furthermore, the reaction is still so selective that only one product can be detected. Once the selective attack on one substrate nucleus has occurred the geometric relationships prohibit further attack on that nucleus, so multiple reactions within a single system do not lead to loss of selectivity.

Two examples have been examined so far. In the best of these, a *m*-iodophenyl template was attached to 3α-cholestanol by preparing the silyl ether **1**. Reaction of *m*-diiodobenzene with

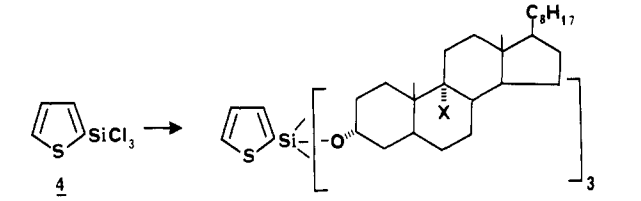


1 X:H
3 X:Cl

2

1 equiv of butyllithium at −78 °C followed by tetraethoxysilane at 0 °C afforded (*m*-iodophenyl)triethoxysilane (**2**).[6] This was converted to the cholestanyl ether **1**[7] by heating with 3α-cholestanol in xylene with a catalytic amount of camphorsulfonic acid. When **1** was irradiated in methylene chloride solution at 25 °C with 3.6 equiv (1.2 equiv/steroid) of sulfuryl chloride[8] and a catalytic amount (5–10 mol %) of AIBN, followed by alkaline hydrolysis accompanied by HCl elimination as we have described previously,[4] the product was 9(11) cholesten-3α-ol in 75–83% yield, with the remainder being unfunctionalized 3α-cholestanol. The material balance was better than 98%, and no other steroid product was detectable. Thus the exclusive functionalization in this case must have been at C-9 to produce the tris(9-chloro) derivative **3**. This is as expected if a chlorine atom becomes attached to the iodine of **1** and then relayed to the hydrogen at C-9. The resulting C-9 radical is then chlorinated by SO_2Cl_2. 3α-Cholestanyl *m*-iodobenzoate used this mechanism[4,5] to direct chlorination to C-9, and models show that the same selectivity is expected for the silyl ether **1**. The high yield, exceeding 66%, indicates that *all three* steroid rings in any given molecule of **1** are being chlorinated as the regenerated template directs a second and then a third selective functionalization.

A related compound was prepared with a thiophene template. We reported earlier[9] that the sulfur atom of diphenyl sulfide could serve as a template for radical-relay chlorinations and also found[10] that the sulfur of thiophene can play such a role. 2-Bromothiophene was converted to the Grignard reagent, and this was reacted with silicon tetrachloride. The resulting trichlorosilane **4** was reacted with 3α-cholestanol to produce the cholestanyl silyl



4

5 X:H
6 X:Cl

ether **5**.[11] When this was irradiated for 2 h in methylene chloride solution with 2 equiv of sulfuryl chloride (with AIBN), it produced a 45% yield of the 9(11)-olefin after alkaline hydrolysis and elimination and 55% recovered cholestanol. Here too no significant formation of any other chlorinated product was observed, and the yield is high enough to indicate that more than one steroid nucleus is being attacked by template control to form **6** and **5**/**6** hybrids. However, it is apparent that at least under these conditions the thiophene template is not as useful as the iodophenyl template, which gives higher yields with less chlorinating agent.

In both of these cases a template-directed reaction is certainly occurring, since halogenations in the absence of a template effect would have led[4] to significant amounts of attack at C-14 and other positions and not just at C-9. Furthermore, the thiophene results indicate that it can be a specific halogen-delivering template, presumably by coordinating a chlorine atom to the sulfur on the thiophene ring. However, the principal importance of our findings is the demonstration that templates can indeed act repeatedly to functionalize several substrate molecules, without any loss of specificity. In addition, since all the previous examples of template-directed halogenation have involved the attachment of the template to the substrate as a simple carboxylic ester, it is interesting to see that this is not necessary for selective reaction to occur. Silyl ethers are frequently preparable from hindered alcohols in which esterification is difficult, so the observation that silicon-based templates can be used may broaden the scope of these methods. The finding that three substrates can be attacked for each template used may also make the methods even more attractive for practical application.[12,13]

(6) Bp 94–96 °C (0.2 mm); M + 1 366; anal. C, H, S, Si; ^{1}H NMR δ 7.97–7.07 (4 H), 3.84 (q, 6 H), 0.71 (t, 9 H).

(7) Mp 167–168 °C; M$^+$ 1394; ^{1}H NMR δ 4.23 (3β-H), 0.75 (18-Me), 0.63 (19-Me).

(8) We have described[4] the use of either SO_2Cl_2 or phenyliodine dichloride as chlorine sources for radical-relay chlorinations. Usually the two were equally useful, but in the present case SO_2Cl_2 is the superior reagent.

(9) Breslow, R.; Wife, R. L.; Prezant, D. *Tetrahedron Lett.* **1976**, 1925.

(10) Prezant, D., unpublished work.

(11) Mp 123–126 °C; M$^+$ 1274; anal. C, H, S, Si; ^{1}H NMR δ 7.65–7.20 (3 H), 4.25 (3-β-H), 0.75 (18-Me), 0.63 (19-Me).

(12) For a recent example of such applications in other laboratories, see: Kerb, U.; Stahnke, M.; Schulze, P.-E.; Wiechert, R. *Angew. Chem., Int. Ed., Engl.* **1981**, *20*, 88–89.

(13) Support of this work by the National Science Foundation is gratefully acknowledged.

Studies in Macrolide Synthesis: Lactones by S to O Acyl Transfer of Hydroxyalkyl Thiol Lactones

E. Vedejs* and D. W. Powell

S. M. McElvain Laboratory of Organic Chemistry and Chemistry Department, University of Wisconsin Madison, Wisconsin 53706

Received December 14, 1981

We report a new method for the synthesis of medium-ring lactones from cyclic sulfide precursors. The essential features of this technique are illustrated in a synthesis of phoracantholide I (**11**, Scheme I).[1]

In the first nontrivial step, **5a** is converted into **7a**[2] (83%) by heating with K_2CO_3 in acetonitrile. This step is based on analogous ring-forming reactions that have been studied in our laboratory and is believed to occur by 2,3 sigmatropic shift of an intermediate ylide **6**.[3]

After double-bond reduction (diimide) and protecting-group manipulation, the phosphine oxide **8a** is converted into the key thiol lactone **9a**[4] (62%) by reaction with C_4H_9Li followed by

(1) Previous syntheses of phoracantholide I: Gerlach, A.; Kunzler, P.; Ortle, K. *Helv. Chim. Acta* **1978**, *61*, 1226. Malherbe, R.; Bellus, D.; *Ibid.* **1978**, *61*, 3096. Petrzilka, M. *Ibid.* **1978**, *61*, 3075. Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424. Trost, B. M.; Verhoeven, T. R. *Ibid.* **1979**, *101*, 1595.

(2) **7a** (mixture of diastereomers), major diastereomer: mp 184–185 °C (crystallized from ethyl acetate–hexane); NMR spectrum (vinyl region) shows two atropisomers frozen out on NMR time scale, 270 MHz ($CDCl_3$) δ 5.7 (1 H, both atropisomers overlapping, m), 5.47 (0.33 H, ddd, J = 15.4, 9.7, 4.1 Hz), 5.13 (0.67 H, J = 15.4, 10.7, 4.8 Hz).

(3) Vedejs, E.; Gapinski, D. M.; Hagen, J. P. *J. Org. Chem.* **1981**, *46*, 5452.

(4) **9a** (oil after preparative TLC): NMR (270 MHz) δ 4.05 (1 H, m), 3.69 (1 H, dt, J = 11.0, 4.0 Hz), 2.78 (1 H, ddd, J = 12.9, 8.8, 4.0 Hz), 2.61 (1 H, ddd, J = 12.9, 7.7, 4.0 Hz), 1.2–2.13 (11, H, complex), 1.23 (3 H, d, J = 6.6); IR (neat) 1660 cm^{-1}.

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