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Addition Reaction of *gem*-Dichloroallyl Lithium to Benzophenones in the Presence of Macrocyclic Ligands: Formation of Chloro Oxiranes

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Abstract: Benzophenones selectively attack the γ unsubstituted terminus of *gem*-dichloroallyl lithium, but show an increasing opposite selectivity for the α terminus in the presence of 12-crown-4 and cryptand [2.1.1]. The products coming from the α addition reaction undergo epoxidation by internal S_n reaction at -95 °C. *Ab initio* theoretical computations on the corresponding transition structures are also reported and discussed.

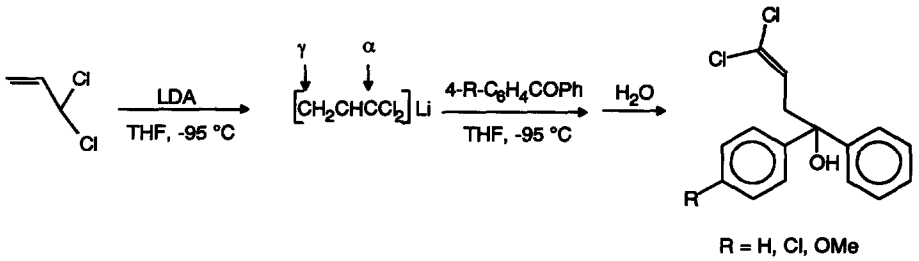
gem-Dichloroallyl lithium has been prepared by Seyferth, Mauzé and co-workers utilising the reaction of *n*-butyllithium with 3,3-dichloroallyltriphenyl lead. The reactivity of this anionic species with different electrophiles has been also studied by the same authors:[1] it reacts with metallic and metalloidal halides, and with aldehydes and ketones yielding different products that are characteristic of the reaction at both termini of the delocalised system, ranging from a complete α attack to a complete γ attack. On the other hand we have studied the regioselectivity of *gem*-dichloroallyl anion with substituted benzaldehydes as a function of the presence of the complexing agent of the lithium cation 12-crown-4, and proposed a rationalisation of the experimental results on the basis of theoretical *ab initio* computational data.[2] The effect of the nature of the counterion (lithium, sodium or potassium) has also been investigated both by an experimental and theoretical point of view.[3]

The purpose of the present paper is to describe the addition reaction of lithiated 3,3-dichloropropenide to substituted benzophenones in the absence and in the presence of 12-crown-4[4] and cryptand [2.1.1],[5] which take place according to a mechanism different from that previously reported for benzaldehydes and acetophenone.[2] A possible rationalisation of the experimental regioselectivity, on the basis of *ab initio* computational data, is also proposed.

RESULTS AND DISCUSSION

Treatment of acrolein with an equivalent amount of $POCl_5$ in xylene yielded 3,3-dichloropropene.[6] This intermediate cannot be directly treated with *n*-BuLi or LDA in THF even at low temperatures, owing to the extreme thermolability of the produced *gem*-dichloroallylithium.[1(c)] On the other hand, addition of an equimolecular mixture of 3,3-dichloropropene and benzophenone in THF to a cooled (- 95 °C) solution of LDA

in THF gives 4,4-dichloro-1,1-diphenylbut-3-en-1-ol. The product results from a regioselective addition of the γ terminus of the produced *gem*-dichloroallyl lithium to the carbonyl group, according to the reaction depicted in Scheme 1.



Scheme 1. Selective γ-addition pathway of *gem*-dichloroallyl lithium to benzophenones.

Table 1. Reaction of *gem*-Dichloroallyl Lithium with Substituted Benzophenones in the Absence of Macrocyclic Ligands.[a]

Carbonyl Compound	Yield (%)[b]	α:γ Ratio[c]
PhCOPh	70	< 1 : 100
4-Cl-C_6H_4COPh	50	< 1 : 100
4-MeO-C_6H_4COPh	60	< 1 : 100

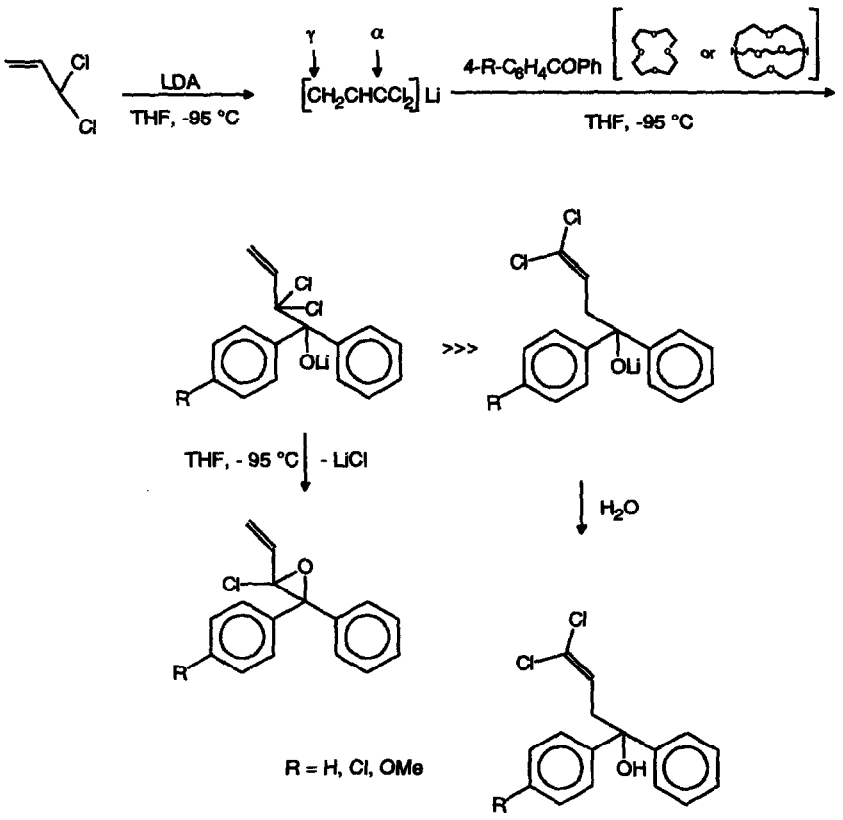
[a]3,3-Dichloropropene, 5.0 mmol; carbonyl compound, 4.5 mmol; LDA, 5.0 mmol; THF, 10 ml; T = -95 °C. [b]Isolated product. [c]By ^{1}H NMR and GC, on the crude reaction product.

Table 2. Reaction of *gem*-Dichloroallyl Lithium with Substituted Benzophenones in the Presence of 12-Crown-4 and Cryptand [2.1.1].

Carbonyl Compound	12-Crown-4[a]		Cryptand [2.1.1][b]	
	Yield (%)[c]	α:γ Ratio[d]	Yield (%)[c]	α:γ Ratio[d]
PhCOPh	50	90 : 10	40	100 : < 1
4-Cl-C_6H_4COPh	30	90 : 10		
4-MeO-C_6H_4COPh	40	90 : 10		

[a]12-Crown-4, 5.0 mmol; 3,3-dichloropropene, 5.0 mmol; carbonyl compound, 4.5 mmol; LDA, 5.0 mmol; THF, 10 ml; T = -95 °C. [b]Cryptand [2.1.1], 1.25 mmol; 3,3-dichloropropene, 1.25 mmol; carbonyl compound, 1.20 mmol; LDA, 1.25 mmol; THF, 2.5 ml; T = -95 °C. [c]Isolated product (α + γ). [d]By ^{1}H NMR and GC, on the crude reaction product.

On the contrary, when the addition reaction is carried out under analogous experimental conditions, but in the presence of a macrocyclic ligand specific for the lithium cation (12-crown-4 or cryptand [2.1.1]), the reaction outcome inverts, and the α terminus becomes progressively the preferential reaction site, as shown in Scheme 2.



Scheme 2. Formation of chloro oxiranes by α-addition pathway of *gem*-dichloroallyl lithium to benzophenones.

The results of the reaction of *gem*-dichloroallyl lithium with benzophenones, both in the absence and in the presence of macrocyclic ligands, are reported in Table 1 and 2 respectively.

In the absence of the complexing agents the regioselective attack to the γ site is observed; comparable results have been obtained and discussed by other authors when studying similar reactions,[1(c),(g), 7] and in our laboratory.[2, 3] The presence of 12-crown-4 and cryptand [2.1.1] changes significantly the reaction outcome, with a sharp increase in the α regioselectivity. Moreover, the binding properties of the complexing agent clearly affect the trend of the increasing selectivity for the substituted CCl_2 terminus. In fact, in the presence of the macrobicyclic ligand, that is known to have more pronounced receptor properties for the lithium cation than the corresponding monocyclic crown ether,[8] no detectable amounts of the product coming from the attack to the CH_2 unsubstituted terminus was detected. On the other hand, in the case of 12-crown-4, the products

corresponding to the reactions at both termini of the allylic system are still present (α : γ ratio = 90 : 10). An analogous behaviour of *gem*-dichloroallyl lithium in reactions with substituted benzaldehydes and acetophenone, in the presence of 12-crown-4 has been previously reported.[2] In the same paper we have proposed a possible rationalisation of the experimental clearcut preference for the α attack on the basis of *ab initio* computational data.

In the present paper we attempt to model the experimental conditions of the reaction in the presence of the complexing agents considering a free $[CH_2CHCCl_2]^-$ anion interacting with a H_2CO molecule. In Figure 1 an electrostatic complex is shown, in which the *gem*-dichloroallyl anion and the aldehyde interact quite weakly at a distance of 3.216 Å. The energy difference between the two separated fragments and the electrostatic complex is 33.7 kcal mol^{-1}. Moreover the geometrical parameters of the two fragments in the complex are close to those in the corresponding isolated species. In Figures 2 and 3 are shown the transition structures for an α and γ attack, respectively. In the case of the transition structure corresponding to the α attack, we note only minor differences with the σ-complex structure, except for the parameters more involved in the transition structure eigenvector of the Hessian matrix, *i.e.* the distance between the Cα and the carbonyl carbon (shortened to 2.200 Å). The CO bond is also lengthened to 1.237 Å. These minor changes in structure reflect in an activation energy barrier of 5.4 kcal mol^{-1}. On the other hand the γ-attack transition structure involves major changes in all the geometrical parameters in that the allylic moiety appears "inverted" with respect to the σ-complex: the Cα-Cβ bond length resembles now a double bond while the Cβ-Cγ bond length is closer to a single bond with the consequent pyramidalization of the CH_2 terminus. We know from a previous work that the α-pyramidalized structure is an absolute minimum for the $[CH_2CHCCl_2]^-$ anion.[3b] The Cγ-C carbonyl distance is 2.059 Å and the C-O distance is 1.257 Å, which reflects in a "later" character of the γ-transition structure with respect to the α-transition structure. The free energy barrier for the γ-attack results to be 17.4 kcal mol^{-1}. On the contrary the corresponding energy barriers for the lithiated structures appear to be comparable.[9] In the lithiated γ-transition structure the lithium cation strongly interacts with the CCl_2 terminus which maintains a degree of pyramidalization. This represents an extra stabilisation which adds to the major effect of electrostatic interactions with the negatively charged centre. This simple model is consistent with the change in regioselectivity being caused by an effective complexation of the lithium cation by the macrocyclic ligands.

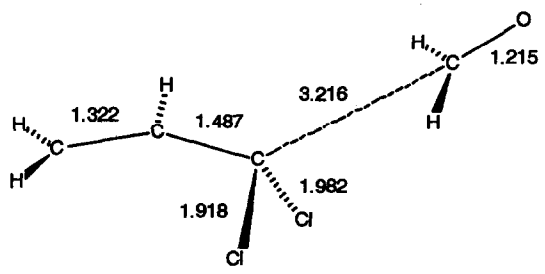


Figure 1. σ-Complex for the addition reaction of *gem*-dichloroallyl anion to formaldehyde. Bond lengths in ångströms.

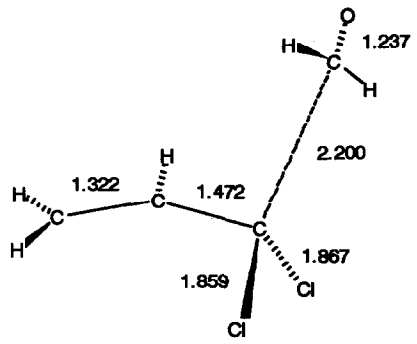


Figure 2. Transition structure for the α-addition pathway of *gem*-dichloroallyl anion to formaldehyde. Bond lengths in ångströms.

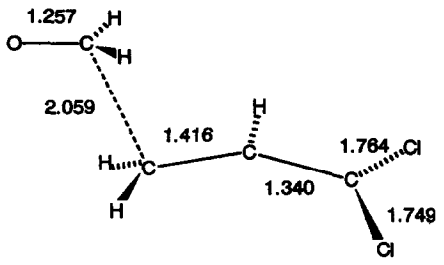


Figure 3. Transition structure for the γ-addition pathway of *gem*-dichloroallyl anion to formaldehyde. Bond length in ångströms.

Moreover, the reaction carried out in the presence of the macrocyclic ligands gives directly a vinyl substituted epoxide. Formation of epoxides from the primary adducts of lithium halocarbenoids to aldehydes or ketones (a formal carbene addition to the carbonyl group) has been previously reported.[10] In particular, Mauzé has reported that vinyl substituted epoxides and β-vinyl substituted alcohols were obtained by reaction of chloroallyl lithium with aldehydes and ketones.[7] It must be noted that in the Mauzé's work the reaction temperature increases from -90 to 20 °C, and in particular, chloroallyllithium and benzophenone give selectively the β-vinyl substituted alcohol, coming from the γ attack.

The results here reported indicate that the presence of the lithium complexing agent inverts the regioselective outcome of the addition reaction, and at the same time facilitates the S_n reaction that leads to the epoxide. Both the effects can be attributed to the weakening of the ionic C-Li[11] and O-Li bonds, that is induced by the binding properties of the ligand. The complexation produces a twofold effect: firstly, it promotes α selectivity,[12] and secondly, removing the counterion from the produced lithium alkoxide, it favours the ring closure to epoxide through internal S_n reaction, even at -95 °C.[13] We have verified that the ring closure takes place at -95 °C by quenching the reaction at this temperature with an excess of $(CH_3)_3ClSi$: no detectable amount of silylated alcohol was obtained. The facile ring closure can be probably also promoted by the steric hindrance of the two phenyl groups: in fact, in the case of analogous reactions under similar experimental conditions with substitute benzaldehydes, the silylated alcohols were isolated.[3a] It must be moreover noted, comparing the data in Tables 1 and 2, that the reaction yields are remarkably lowered for the reactions carried out in the presence of the macrocyclic ligands, in comparison with those obtained in their absence. Such effect indicates that the co-ordination of the cation at the carbonyl group is a fundamental step of the addition reaction.[14]

EXPERIMENTAL SECTION

3,3-Dichloropropene was synthesised according to the literature.[6] All the reaction of *gem*-dichloroallyl lithium were carried out in THF at -95 °C, according to an *in situ* procedure.[2, 15] THF was dried by distillation from benzophenone ketyl, LDA was prepared according to standard procedure,[16] 12-crown-4 and cryptand [2.1.1] were purchased from Aldrich. All chemicals commercially available were reagent grade and were used without further purification. ^{1}H NMR spectra were recorded on a Hitachi Perkin Helmer R-24B 60 MHz in $CDCl_3$, using TMS as internal standard. Infrared spectra were run on a Perkin-Elmer 599B spectrophotometer. Reaction products obtained in the absence of the complexing agents, were purified by preparative column chromatography on Merck Kieselgel 60 with diethyl ether-light petroleum (30-60) as an eluant (20 : 80); a 5 : 95 mixture was used for products obtained in the presence of the macrocyclic ligands. Same pertinent data for the synthesised compounds are listed below. All the alcohols show, by IR analysis, the following bands (cm^{-1}): 3470-3460 (OH) and 1650 ($CH=CCl_2$); the tetrasubstituted epoxides: 3080, 1650, 990, 930 ($CH=CH_2$) and one or more bands in the range 905-825 (C-O-C).

4,4-Dichloro-1,1-diphenylbut-3-en-1-ol. ^{1}H NMR δ_H ($CDCl_3$, Me_4Si) 3.10 (2 H, d, J = 7 Hz, CH_2), 3.50 (1 H, br s, O*H*), 5.80 (1 H, t, J = 7 Hz, -*H*C=), 7.10-7.60 (10 H, br s, $(C_6H_5)_2$). Anal. Calcd. for $C_{16}H_{14}Cl_2O$: C, 65.55; H, 4.81. Found: C, 65.0; H, 4.9 %.

4,4-Dichloro-1-phenyl-1-(4-chlorophenyl)but-3-en-1-ol. ^{1}H NMR δ_H ($CDCl_3$, Me_4Si) 3.15 (2 H, d, J = 7 Hz, CH_2), 3.10 (1 H, br s, O*H*), 5.90 (1 H, t, J = 7 Hz, -*H*C=), 7.00-7.75 (9 H, m, C_6H_5, ClC_6H_4). Anal. Calcd. for $C_{16}H_{13}Cl_3O$: C, 58.66; H, 4.00. Found: C, 58.0; H, 4.2 %.

4,4-Dichloro-1-phenyl-1-(4-methoxyphenyl)but-3-en-1-ol. ^{1}H NMR δ_H ($CDCl_3$, Me_4Si) 2.90 (1 H, br s, O*H*), 3.10 (2 H, d, J = 7 Hz, CH_2), 3.75 (3 H, s, CH_3O), 5.80 (1 H, t, J 7 Hz, -*H*C=), 7.00-7.40 (9 H, m, C_6H_5, $MeOC_6H_4$). Anal. Calcd. for $C_{17}H_{16}O_2Cl_2$: C, 63.17; H, 4.99. Found: C, 62.8; H, 4.9 %.

3-Chloro-4,4-diphenyl-3,4-epoxibut-1-ene. ^{1}H NMR δ_H ($CDCl_3$, Me_4Si) 5.75 (1 H, dd, J = 10, 2 Hz, =CH*H cis*), 6.50 (1 H, dd, J = 16, 2 Hz, =CH*H trans*), 6.75 (1 H, dd, J = 16, 10 Hz, -*H*C=), 7.30 (10 H, br s, $(C_6H_5)_2$). Anal. Calcd. for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10. Found: C, 75.2; H, 5.0 %.

3-Chloro-4-phenyl-4-(4-chlorophenyl)-3,4-epoxibut-1-ene. ^{1}H NMR δ_H ($CDCl_3$, Me_4Si) 5.75 (1 H, dd, J = 10, 2 Hz, =CH*H cis*), 6.50 (1 H, dd, J = 16, 2 Hz, =CH*H trans*), 6.75 (1 H, dd, J 16, 10 Hz, -*H*C=), 7.20-7.40 (9 H, m, C_6H_5, ClC_6H_4) Anal. Calcd. for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.15. Found: C, 66.2; H, 4.4 %.

3-Chloro-4-phenyl-4-(4-methoxyphenyl)-3,4-epoxibut-1-ene. ^{1}H NMR δ_H ($CDCl_3$, Me_4Si) 3.70 (3 H, s, CH_3O), 5.80 (1 H, dd, J = 10, 1.5 Hz, =CH*H cis*), 6.60 (1 H, dd, J = 16, 1.5 Hz, =CH*H trans*), 6.75 (1 H, dd, J = 16, 10 Hz, -*H*C=), 7.00-7.40 (9 H, m, C_6H_5, $MeOC_6H_4$). Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.31; H, 5.28. Found: C, 71.4; H, 5.4.

METHODS

The stationary points were determined by complete optimisation of the geometrical parameters by gradient methods. The computations were done at the RHF level of theory using the 3-21G basis set with d function on chlorine. The critical points have been characterised by computations of the vibrational frequencies at the same level of theory. The computation were performed using the GAUSSIAN92[17] series of programs on an IBM RISC-6000/550 computer. The thermodynamic data have been computed at 183 K using the standard statistical thermodynamic formula. The -TΔS contributions 2.5 and 2.7 Kcal mol^{-1} for the α and γ attack to the $\Delta G^{\neq}$ do not alter the picture obtained by simply taking into account the potential energy barrier.

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12. For a detailed discussion of the effects of the cation complexation on the reaction regioselectivity on the basis of computational data, see ref. 2.

13. Dihalocarbenes and carbenoids do not generally add to the C=O bonds of ordinary aldehydes and ketones; for exception see: Greuter, H.; Winkler, T.; Bellus, D. *Helv. Chim. Acta* **1979**, *62*, 1275-1282. Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795-798. Araki, S.; Butsugan, Y. *J. Chem. Soc, Chem. Comun.* **1989**, 1286-1287. We have checked the formation of carbenoid species performing the reaction in the presence of *trans*-stilbene or cyclohexene: neither in the absence of 12-crown-4, nor in its presence, the products deriving from the addition of carbenoid intermediates to the C-C double bond were detected.

14. Cation-assisted reactions are handicapped by complexation. Decreases of the reaction rates of the reduction of carbonyl groups by metal hydrides (see for example Handel, H.; Pierre, J. *Tetrahedron Lett.* **1976**, 741-744, and Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* **1976**, 1677-1680), and of the addition of organic lithium compounds (Pierre, J. L.; Handel, H.; Perraud, R. *Tetrahedron Lett.* **1977**, 2013-2014) have been reported in the presence of crown compounds.

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