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Chloroallyl Anion : Highly Regio- and Diastereoselective α-Addition of Chloroallyl Zinc Reagent to Carbonyl Compounds

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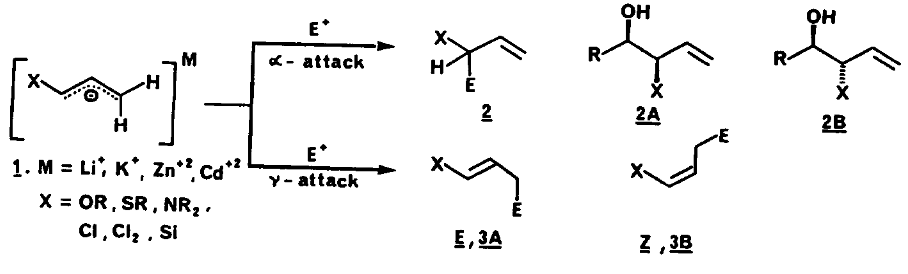
Abstract: The chloroallyl zinc reagent generated *insitu* by deprotonation of allyl chloride in the presence of lithium diisopropylamide and zinc chloride undergoes highly regio- and diastereoselective α-addition to carbonyl compounds to give *syn* chlorohydrins which on treatment with base afford *cis* vinyloxiranes in high yields.

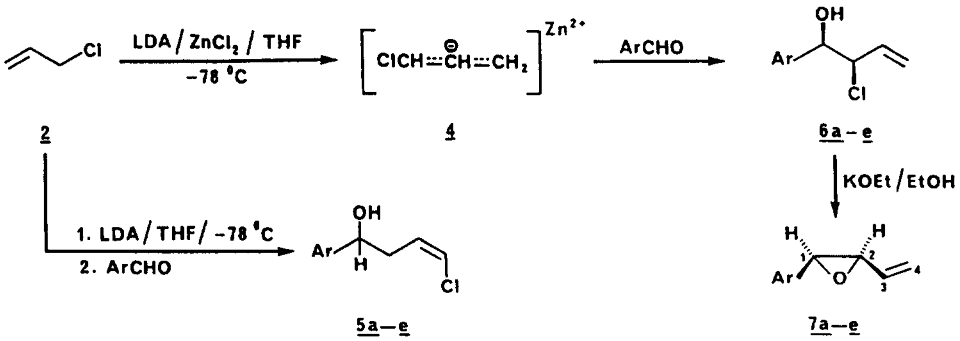
Heteroatom substituted allyl anions react with electrophiles to give products that are characteristic of reactions of both *termini* (α/ γ) of the propenylic system (Scheme 1)[1]. Many innovative workers have examined the stereo- and regiocontrolled addition of allylic anions to carbonyl compounds with varying degree of success. Seyferth and coworkers[2] have investigated the influence of electronic factors on α/ γ selectivity in the reaction of *gem*-dichloroallyllithium (obtained by the action of n-butyllithium on 3,3-dichloroallyltriphenyllead in THF at -95°C) with several carbonyl compounds. More recently Venturello and co-workers[3] obtained high degree of α-regioselectivity when *gem*-dichloroallyllithium was added to aromatic aldehydes in the presence of potassium *t*-butoxide. The reactions of chloroallyllithium with different electrophiles and their synthetic utility have been examined by Mauze and co-workers[4]. Yamamoto and co-workers[5] have reported regioselectivity control in the reactions of alkoxy and alkylthio substituted carbanions *via* aluminium 'ate' complexes. The α/ γ selectivity has been shown to be dramatically counter ion dependent and high degree of α-regioselectivity has been thus achieved in the reactions of heteroatom substituted allyl zinc[6,7], allyl cadmium[8] and allyl potassium[3] derivatives with carbonyl compounds. Despite these efforts, the problem of α/ γ selectivity in these species still remains unresolved[9]. There are other dimensions associated with this problem. Firstly, even if the γ-adduct **3** can be generated preferentially, further selectivity is desired with respect to *E* or *Z* (**3A** or **3B**) configuration of double bond (Scheme 1). Secondly, the α-addition of **1** to carbonyl compounds may also yield a mixture of expected diastereomers **2A** or **2B**, although it would be more useful in preparative chemistry if only one of the two isomers is formed. Stereoselective routes for **3A** or **3B** (X=N,O,S,Si, halogen) have been developed [10], whereas not much attention has been paid to study diastereoselectivity



Scheme 1

in the α-addition of 1 to carbonyl compounds[11]. We wish to report in this communication that chloroallyl anion generated *insitu* by deprotonation of allyl chloride with lithium diisopropylamide (LDA) in the presence of zinc chloride, reacts with carbonyl compounds in highly regioselective manner to give α-adducts (chlorohydrins) in high yields. Further, the reaction of 1 with aromatic aldehydes under these conditions is found to be highly diastereoselective to give only *syn* isomers 2A, which on treatment with base afford only *cis* vinyloxiranes in high yields.

The addition of chloroallyllithium (generated by deprotonation of allyl chloride with LDA at -78°C) with aromatic aldehydes was first examined and the results are shown in the Table I. Apparently the γ-adducts (Z) are formed predominantly in all the cases (5a-e) studied in 51-76% overall yields. These results are in accordance with those of earlier workers[4a]. In order to obtain α-adducts, the metallation reaction was carried out with LDA in the presence of zinc chloride and the resulting allylic zinc reagent was allowed to react *insitu* with aromatic aldehydes. Results obtained indicated that only α-adducts (6a-e)were formed (Table I) (Scheme 2). The reaction was found to be highly diastereoselective also yielding only the *syn* isomers. This was evident from the ^{1}H NMR spectrum of α- adducts 6a-e[12] which was further supported by the analysis of the corresponding vinyloxiranes 7a-e obtained by treatment of these adducts with base. Treatment of 6a with ethanolic potassium ethoxide yielded only *cis* vinyloxirane 7a (96%) which was recognized by the appearance of a sharp doublet at δ 4.09 (J=4 *Hz*) and a triplet at



Scheme 2

Table I. Reactions of Chloroallyl Anion with Aldehydes.

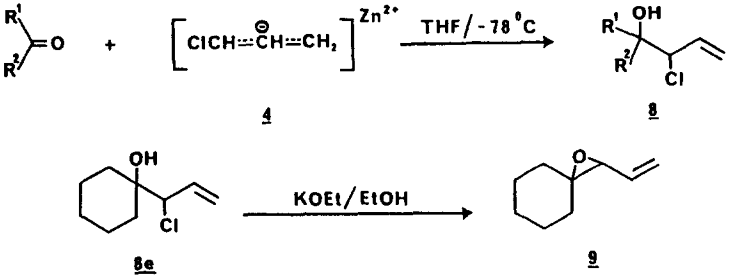
Entry	Carbonyl Compounds	LDA % yield[a]	LDA/$ZnCl_2$ % yield[a,b]	Oxiranes % yield[a]
1	C_6H_5CHO	5a 68	6a 80 (96)	7a 98
2	4-ClC_6H_4CHO	5b 76	6b 65 (95)	7b 97
3	4-$MeOC_6H_4CHO$	5c 73	6c 62 (96)	7c 95
4	4-MeC_6H_4CHO	5d 61	6d 67 (94)	7d 96
5	2-ClC_6H_4CHO	5e 51	6e 52 (93)	7e 94
6	MeCHO	-	6f 78 (78)	-

[a] All products were characterised with the help of spectral and analytical data.

[b] In all the cases, only α-adducts were formed and starting aldehydes were recovered. Figure in parenthesis report yields on the basis of recovered aldehyde.

δ 3.56 (J=4.2Hz) due to H-1 and H-2 proton resonance respectively[13]. The corresponding *trans* isomer could not be detected from the reaction mixture. The other α-adducts **6b-e** similarly afforded only *cis* vinyloxiranes **7b-e** in nearly quantitative yields. Similar addition of **4** to aliphatic aldehydes did not afford the clear products and only the α-adduct **6f** from acetaldehyde could be isolated in 78% yield.

High α-regioselectivity was also observed when **4** was reacted with acyclic and cyclic ketones under the described conditions (LDA/ZnCl$_2$) to afford the corresponding chlorohydrins **8a-e** in 61-73% overall yields (Table II). As a typical example, one of the chlorohydrins **8e** was converted to the corresponding oxirane **9** in 96% yield by treatment with ethanolic potassium ethoxide as described earlier (Scheme 3).



Scheme 3

The reaction thus provides a new entry to chlorohydrins and the corresponding vinyloxiranes in highly stereo- and regioselective manner through C-C bond formation. It is pertinent to note that the earlier workers failed to isolate chlorohydrins in the reactions of chloroallyllithium with carbonyl compounds and only the epoxides were obtained as the final products[4h]. The detailed study of the reaction and its synthetic utility is under investigation.

The following general experimental procedure is representative of this conversion. To a solution/suspension of freshly fused zinc chloride (1.40g, 10 mmol) in dry THF (150 mL) at -78°C(under nitrogen atmosphere) was added allyl chloride (0.50g, 7.5 mmol). Preformed LDA [10 mmol, prepared from BuLi (10 mmol) in ether (10 mL) and diisopropylamine (1.0g, 10 mmol) in 10 mL of dry THF, stirred at 0°C for 0.5 hr] was added dropwise during 20 min followed by stirring (10 min) and addition of carbonyl compound (5 mmol). The reaction mixture was quenched after 0.5 h with sat. NaHCO$_3$ solution (100 mL) at the same temperature, extracted with ether, dried (Na$_2$SO$_4$) and concentrated to give the crude chlorohydrins which were purified by passing through silica gel column using hexane/EtOAc as eluent (Table I).

Table II. Reactions of Chloroallyl Anion with Ketones (LDA/ZnCl$_2$).

Entry	Ketone		% yield 8^{a,b}
1	CH_3COCH_3	8a	64 (64)
2	$CH_3COCH_2CH_3$	8b	61 (61)
3	$C_6H_5COCH_3$	8c	62 (95)
4	$C_6H_5COC_6H_5$	8d	68 (96)
5	Cyclohexanone	8e	73 (93)

a All the products were characterised with the help of spectral and analytical data

b Figure in parenthesis report yields on the basis of recovered ketone.

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12. ^{1}H NMR spectra of α-adducts **6a-e** exhibited sharp signals for all the protons showing the presence of only one diastereomer; **6b** : Colourless oil; IR(neat): 3600,3400,1620,1500,1415,1190,1095,930 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$); 3.21 (brs, 1H, $O\underline{H}$); 4.45 (dd, 1H, J=7.0,7.5 *Hz*, $C\underline{H}Cl$); 4.64 (d, 1H, J=7.0 *Hz*, $C\underline{H}OH$); 5.10 (d, 1H, J=10 *Hz*, $=C\underline{H}_2$); 5.15 (d, 1H, J=17.5 *Hz*, $=C\underline{H}_2$); 5.74 (dd d, 1H, J=17.5,10,7.5 *Hz*, $CH-C\underline{H}=$); 7.22-7.30(m, 4H, Arom). ^{13}C NMR ($CDCl_3$): 68.79 ($\underline{C}H$); 76.5 ($\underline{C}H$); 119.65 ($=\underline{C}H_2$); 128.30 ($\underline{C}H$,Ar); 128.46 ($\underline{C}H$,Ar); 133.95 ($-\underline{C}H=CH_2$); 134.10 (C-1', Arom); 137.6 (C-4', Arom).

    7b : Colourless oil; IR(neat): 1500,1448,1420,1270 cm^{-1}. ^{1}H NMR (90 MHz, CCl_4): δ 3.58 (t, J=4.2 *Hz*, 1H, H-2); 4.19 (d, J=4 *Hz*, 1H, H-1); 5.14-5.68 (m, 3H, $C\underline{H}=C\underline{H}_2$); 7.36 (s, 4H, $Ar\underline{H}$).

    8e: Colourless oil; IR(neat): 3600,3500,1459,1360,1258,1179 cm^{-1}. ^{1}H NMR (90 MHz, CCl_4): δ 1.05-2.15 (br m, 10H, ring $C\underline{H}_2$); 3.70 (brs, 1H, $O\underline{H}$ exchangeable with D_2O); 4.25 (d, J=9 *Hz*, 1H, $C\underline{H}Cl$); 5.12-5.45 (m, 2H, $=C\underline{H}_2$); 5.78-6.29 (m, 1H, $-C\underline{H}=CH_2$).

    9: Colourless oil; IR(neat): 1610,1518,1431,1220 cm^{-1}. ^{1}H NMR (90 MHz, CCl_4): δ 1.13-1.85 (m, 10H, ring $C\underline{H}_2$): 2.97 (d, J=5 *Hz*, 1H, $C\underline{H}-O$); 5.07-5.90 (m, 3H, $C\underline{H}=C\underline{H}_2$).
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