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Reactivity of γ-chloro-*gem*-trichloroalkanes with chromous chloride

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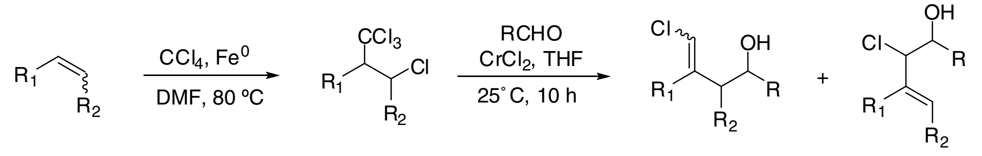
Abstract—$CrCl_2$-mediated condensation of γ-chloro-*gem*-trichloroalkanes with aldehyde generates homoallylic alcohols through a hydride rearrangement followed by a Nozaki–Hiyama allylation.

Organochromium reagents have emerged as versatile synthetic intermediates due in large part to their unique stereo-, regio- and chemo-selectivities. In the Hiyama–Nozaki allylation, allylchromium(III) reagents, most commonly made from allylic halides utilizing $CrCl_2$, have proven useful for the preparation of homoallylic alcohols under mild conditions.[1] On the other hand, the initial dichlorochromium(III) carbenoid generated from *gem*-trichlorides often undergoes further metallation to a chlorodichromium(III) species, which has found considerable synthetic utility.[2] As part of our continuing investigation of organochromium methodology, we report herein the preparation of homoallylic alcohols from γ-chloro-*gem*-trichloroalkanes with chromous chloride in THF. The intramolecular rearrangement of chromium(III) γ-chloro-alkylidene intermediates was evidenced by isotopic labelling.

γ-Halo-*gem*-trihaloalkanes are easily synthesized via Kharasch addition of polyhaloalkanes to alkenes, catalyzed by various metals.[3] 1-Chloro-2-trichloromethyl-cyclohexane **2a** was prepared from cyclohexene **1a** and tetrachloromethane in the presence of Fe(0) in 53% yield as a mixture (2:1) of *anti*/*syn* isomers (Scheme 1).[4] Purification by reversed-phase chromatography affords pure *anti*-**2a**. 5-Chloro-6-trichloromethyldecane **2b** was synthesized under the same conditions in 48% yield as a mixture (2:1) of *anti*/*syn* isomers.

The reaction of 1-chloro-2-trichloromethyl-cyclohexane **2a** with chromous chloride in the presence of *p*-tolualdehyde **3** gives (*E*-2-chloromethylene-cyclohexyl)-*p*-tolyl-methanol **4a** as a mixture of diastereoisomers (70:30) in 60% yield and 2-chloro-2-cyclohex-1-enyl-1-*p*-tolyl-ethanol **5a** in 3% yield (Scheme 1).[5,6] Purification by



1a $R_1, R_2 = -(CH_2)_4-$
1b $R_1 = R_2 = n$-Bu

2a (53 %, *anti*/*syn* = 2:1)
2b (48 %, *anti*/*syn* = 2:1)

4a (R = Tol, 60 %, *anti*/*syn* = 70:30)
4b (R = *i*-Pr, 43 %, *dr* = 60:40)
4c (R = Tol, 54 %, ratio = 45:30:25)

5a (3 %)
5b (< 2 %)
5c (< 2 %)

Scheme 1. $CrCl_2$-mediated condensation of γ-chloro-*gem*-trichloroalkanes with aldehydes.

Keywords: Carbene; Chromium; Nozaki–Hiyama allylation; Trichloroalkane.

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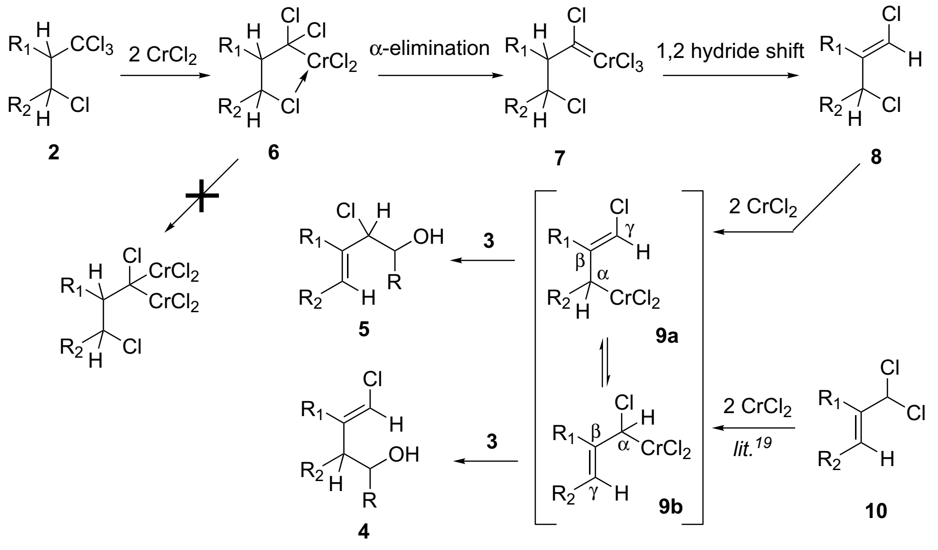
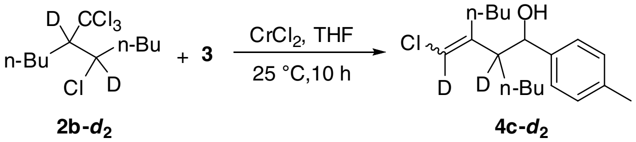


Scheme 2. Proposed mechanism for the reaction of γ-chloro-trichloroalkanes with chromous chloride.

silica gel chromatography afforded the isolated major diastereoisomer **4a** in 30% yield, which was characterized as the *anti* and *E* isomer by X-ray crystallography.[7] The minor isomer **4a** could not be isolated and crystallized, but its *E* stereochemistry was determined by a 2D ^{1}H NOE NMR. Interestingly, the reaction of pure *anti*-**2a** or a mixture (2:1) of *anti*/*syn*-**2a** isomers provides the same ratio of **4a** diastereomers (70:30). Under the same conditions, with isobutyraldehyde **3′**, 1-chloro-2-trichloromethyl-cyclohexane **2a** gives a mixture of **4b** diastereomer (60:40) in 43% yield.[8] 5-Chloro-6-trichloromethyl-decane **2b** in the presence of *p*-tolualdehyde **3** gives homoallylic alcohols **4c** in 54% yield as a mixture (45:30:25) of stereoisomers.[9]

Mechanistically, the formation of **4** and **5** probably proceeds initially through addition of chromium(II) into a C–Cl bond (Scheme 2). Formally, the oxidative addition of Cr(II) involves two consecutive single-electron transfers, thus accounting for 2 equiv of $CrCl_2$ needed for the reduction of one C–Cl bond.[10] Next, the coordination of the γ chlorine atom to the metal most likely induces rehybridization of the dichlorocarbenoid species **6**, thus precluding oxidative addition of $CrCl_2$ into a second *gem*-C–Cl bond.[2b,11] By placing a positive charge in a p orbital, the organochromium produces a tight ion pair, and the formation of a carbene complex **7** is postulated.[12,13] An intramolecular rearrangement involving a 1,2-migration of hydride then gives the allylic chloride intermediate **8**. The hydride migration was demonstrated by reacting 5-chloro-6-trichloro-5,6-d_2-methyldecane **2b-*d*$_2$** under the standard conditions.[14] Using *p*-tolualdehyde and $CrCl_2$, the coupling adduct **4c-*d*$_2$** was obtained (Scheme 3).[15]

Allylic halides in the presence of $CrCl_2$are known to give coupling adducts with aldehydes.[1] Compound **8** reacts with chromium(II) to give the allylchromium(III) reagents **9** and in the presence of an aldehyde, **9** adds to the carbonyl group to furnish homoallylic alcohols **4** and **5**.[16] Whether allylchromium(III) species **9a**(**b**) exists as the η^1 or η^3 structure is not clear, it is likely to be η^1 at least in the transition state of the reaction with carbonyl compound. Allylic metal compounds normally react with carbonyl compounds at the γ position of the allyl metal unit (**9a** → **5** and **9b** → **4**).[17] The results suggest that the alkyl substituents favour the metal at α-position of chlorine to give **9b**, which affords the major coupling adduct **4**. Because of the steric interaction between ligands on chromium and the substituents on the allyl fragment, the equilibrium lies towards the allylic chromium species with less steric crowding of the carbon–chromium bond.[18] As equilibration between two isomeric allylic metal compounds can occur, the allylchromium(III) reagents **9** may also be obtained from 3,3-dichloropropene derivatives **10**.[19]



Scheme 3. $CrCl_2$-mediated condensation of isotopic labelled γ-chloro-*gem*-trichloroalkanes with an aldehyde.

In summary, γ-chloro-*gem*-trichloroalkanes are precursors of α,γ-dichloroallyls and give homoallylic alcohols after further Nozaki–Hiyama reaction. Interestingly, final coupling adducts are obtained through two organochromium intermediates, a dichloro-chromium(III) alkane carbenoid and an allylchromium(III) species, showing a different pattern of transformation owing to the halide at the β position of the trichloromethyl group.

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