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Tetrahedron Letters 47 (2006) 5177–5180
Tetrahedron Letters

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

Steve Tisserand,[a] Romain Bejot,[a] Célia Billaud,[a] De Run Li,[b] J. R. Falck[b,*] and Charles Mioskowski[a,*]

[a]*Laboratoire de Synthèse Bio-Organique, UMR 7175-LC1, Faculté de Pharmacie, Université Louis Pasteur de Strasbourg, 74 Route du Rhin, BP 24, 67401 Illkirch, France*
[b]*Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390-9038, USA*

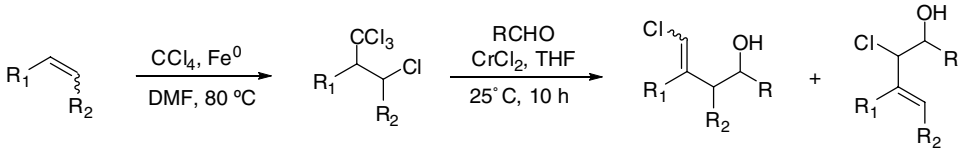
Received 14 March 2006; revised 19 April 2006; accepted 9 May 2006
Available online 5 June 2006

**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** $R_1, R_2 = -(CH_2)_4-$ **2a** (53 %, *anti*/*syn* = 2:1) **4a** (R = Tol, 60 %, *anti*/*syn* = 70:30) **5a** (3 %)
**4b** (R = *i*-Pr, 43 %, *dr* = 60:40) **5b** (< 2 %)
**1b** $R_1 = R_2 = n$-Bu **2b** (48 %, *anti*/*syn* = 2:1) **4c** (R = Tol, 54 %, ratio = 45:30:25) **5c** (< 2 %)

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

*Keywords*: Carbene; Chromium; Nozaki–Hiyama allylation; Trichloroalkane.
* Corresponding authors. E-mail addresses: j.falck@utsouthwestern.edu; mioskow@aspirine.u-strasbg.fr

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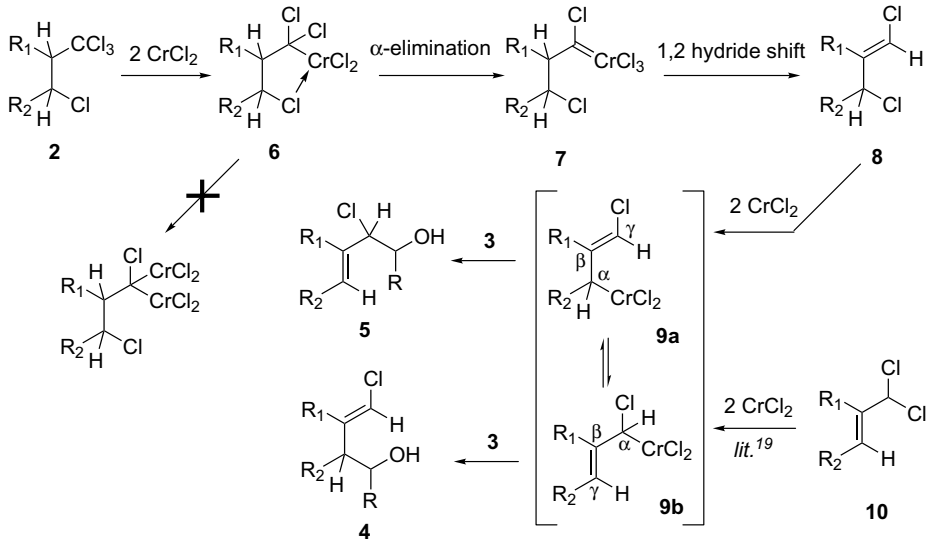
doi:10.1016/j.tetlet.2006.05.045

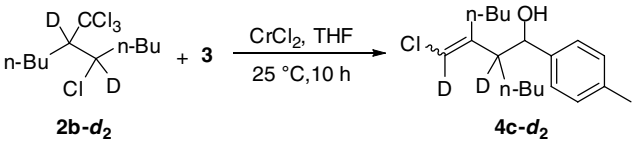



**Scheme 2.** Proposed mechanism for the reaction of γ-chloro-trichloroalkanes with chromous chloride.

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-$d_2$-methyl-decane **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




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

as the $\eta^1$ or $\eta^3$ structure is not clear, it is likely to be $\eta^1$ 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]

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.

## Acknowledgements

This work was supported by the CNRS and the Institut de Recherche Pierre Fabre (S.T.), the Ministère délégué à l'Enseignement supérieur et à la Recherche (R.B.), the Robert A. Welch Foundation and the NIH (GM31278).

We thank Dr. B. Rousseau and the CEA for hydrogenation of 5-decyne with $D_2$, C. Antheaume and Dr. A. De Cian for NMR and X-ray spectroscopy.

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4. Bellesia, F.; Forti, L.; Ghelfi, F.; Pagnoni, U. M. *Synth. Commun.* **1997**, *27*, 961–971, General procedure for the preparation of γ-halo-trihaloalkanes **2a** and **2b**: alkene (22 mmol), iron powder (1.2 g, 44 mmol) and tetrachloromethane (18 mL, 176 mmol) in anhydrous DMF (5 mL) were carefully warmed to 90 °C in a 250 mL round bottom flask, fitted with a condenser (CAUTION: very exothermic reaction). After the reaction started violently, the dark reaction mixture was stirred at 80 °C for 2 h. The reaction was quenched with 5% HCl at rt and extracted with *n*-hexane. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by reversed-phase chromatography ($H_2O$/EtOH = 2:8) afforded **2a** and **2b** as a mixture (2:1) of *anti*/*syn* isomers. Analytical data for **2b**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.75–4.60 (m, 1H), 3.08–2.90 (m, 1H$_{anti}$), 2.59–2.53 (m, 1H$_{syn}$), 2.3–1.2 (m, 12H), 0.96 ppm (t, $J = 7$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 104.1 (C$_{syn}$), 103.1 (C$_{anti}$), 65.4 (C$_{anti}$), 63.3 (C$_{syn}$), 62.6 (C$_{anti}$), 62.3 (C$_{syn}$), 39.0 (C$_{syn}$), 32.7 (C$_{anti}$), 32.2 (C$_{syn}$), 31.9 (C$_{anti}$), 29.4 (C$_{anti}$), 29.1 (C$_{syn}$), 28.5 (C$_{syn}$), 27.5 (C$_{anti}$), 22.9, 22.0, 14.0, 13.8 ppm; MS (CI, $NH_3$) *m*/*z* 295 ([M+H]$^+$), 312 ([M+NH$_4$]$^+$).
5. $CrCl_2$ prepared from $CrCl_3$ via reduction with $Mn^0$ powder. General procedure for the preparation of $CrCl_2$: anhydrous $CrCl_3$ (481 mg, 3.0 mmol) and $Mn^0$ (109 mg, 2.0 mmol) in anhydrous MeCN (4 mL) were stirred at rt for 0.5 h under an argon atmosphere and ultrasound irradiation. The grey and viscous reaction mixture was then concentrated in vacuo and $CrCl_2$ as a grey powder was used for further reaction.
6. General procedure for the preparation of homoallylic alcohols **4** and **5**: to a suspension of $CrCl_2$ (prepared from $CrCl_3$, 3.0 mmol) in anhydrous THF, was added *p*-tolualdehyde (120 mL, 1.0 mmol) and **2** (0.5 mmol), under argon atmosphere at rt. After 10 h stirring at rt, the reaction mixture was quenched with 5% HCl and extracted with $Et_2O$. The ethereal extract was washed with brine, dried over $MgSO_4$, filtered through a small pad of Florisil® and concentrated in vacuo. Purification by column chromatography (*n*-hexane/$Et_2O$ = 95:5) afforded **4** and **5**. Analytical data for *anti*-(*E*)-**4a**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26 (d, 2H, $^3J = 8.1$ Hz), 7.20 (d, 2H, $^3J = 8.1$ Hz), 6.10 (d, 1H, $^4J = 1.5$ Hz), 4.75 (d, 1H, $^3J = 10.3$ Hz), 2.80 (dt, 1H, $^3J = 4.0$ Hz, $^2J = 14.1$ Hz), 2.44 (dt, 1H, $^3J = 4.0$ Hz), 2.38 (s, 3H), 2.17 (ddt, 1H, $^3J = 4.8$ Hz, $^4J = 1.5$ Hz), 1.86 (dquin, 1H, $^3J_1 = {}^3J_2 = 4{,}0$ Hz, $^2J = 12.8$ Hz), 1.64–1.56 (m, 1H), 1.49 (dquin, 1H, $^3J_1 = {}^3J_2 = 4.0$ Hz, $^2J = 13.4$ Hz), 1.41 (dquin, 1H, $^3J_1 = {}^3J_2 = 4.0$ Hz, $^2J = 12.8$ Hz), 1.37–1.27 ppm (m, 2H); $^{13}$C (50 Hz, $CDCl_3$), $\delta$ 142.3, 139.6, 138.1, 129.7, 127.2, 112.3, 73.2, 51.3, 29.6, 27.0, 25.9, 22.6, 21.7 ppm; IR *v* 3442, 2928, 2857, 1743, 1703, 1685, 1607, 1514, 1449, 1296, 1175, 1041, 890, 820, 803, 561, 509 cm$^{-1}$; MS (TOF) *m*/*z* 273 ([M+Na]$^+$). Analytical data for *syn*-*(E)*-**4a**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33 (d, 2H, $^3J = 8.1$ Hz), 7.21 (d, 2H, $^3J = 8.1$ Hz), 6.12 (d, 1H, $^4J = 1.3$ Hz), 4.81 (d, 1H, $^3J = 10.3$ Hz), 3.38–3.30 (m, 1H), 2.49–2.30 (m, 4H), 2.30–1.80 (m, 2H), 1.70–0.95 ppm (m, 5H). Analytical data for **5a**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.95 (s, 1H), 5.56 (dd, 1H, $^3J = 7.8$ Hz, $^4J = 4.0$ Hz), 4.50 (d, 1H, $^3J = 7.8$ Hz), 2.78 ppm (m, 1H); $^3$C (50 Hz, $CDCl_3$), $\delta$ 142.8, 140.4, 138.5, 129.6, 127.4, 113.3, 74.1, 44.7, 30.4, 27.4, 27.1, 23.5, 21.6 ppm.
7. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 295551. Copies of the data can be obtained free of charge, on applicationto CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
8. Compound **4b** was obtained as a mixture (60:40) of diastereomers. Analytical data for **4b**: major isomer: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.94 (d, 1H, $^4J = 1.5$ Hz), 3.68 (dd, 1H, $^3J = 9.8$ Hz, $^3J = 2.2$ Hz), 2.79–2.75 (m, 1H), 2.72–2.68 (m, 1H), 2.27–2.21 (m, 1H), 2.12–1.25 (m, 7H), 1.05 (d, 3H, $^3J = 6.6$ Hz), 0.85 ppm (d, 3H, $^3J = 6.6$ Hz); $^{13}$C (50 Hz, $CDCl_3$) $\delta$ 142.5, 111.4, 72.9, 46.8, 29.0, 28.9, 26.7, 25.6, 22.2, 20.9, 13.7 ppm; minor isomer: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.00 (s, 1H), 3.74 (dd, 1H, $^3J = 10.5$ Hz, $^3J = 2.0$ Hz), 3.13–3.06 (m, 1H), 2.24–1.33 (m, 9H), 1.07 (d, 3H, $^3J = 6.8$ Hz), 0.92 ppm (d, 3H, $^3J = 6.8$ Hz).
9. Compound **4c** was obtained as a mixture (a/b/c = 45:30:25) of stereoisomers. Configuration of stereoisomers could not be determined. Analytical data for **4c**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.5–7.2 (m, 4H, Ar*H*), 6.12 (s, 1H, C=CCCl*H*$_c$), 5.99 (s, 1H, C=CCl*H*$_a$), 5.79 (s, 1H, C=CCCl*H*$_b$), 4.61 (d, $J = 5.6$ Hz, 1H, C*H*OH$_b$), 4.47 (d, $J = 8.6$ Hz, 1H, C*H*OH$_{a\text{ and }c}$), 3.3 (m, 1H, C*H*–CHOH$_c$), 2.4–2.0 (m, 1H, C*H*–CHOH$_{a\text{ and }b}$), 2.34 (s, 3H, ArC*H*$_3$), 2.0–0.7 ppm (m, 22H, C*H*$_3$–(C*H*$_2$)$_4$); $^{13}$C (50 Hz, $CDCl_3$), $\delta$ 142.83, 142.80, 141.8, 140.1, 139.9, 139.5, 137.6, 137.5, 137.0, 129.1, 129.0, 128.8, 127.0, 126.8, 126.1, 125.5, 116.4$_c$, 116.2$_a$, 115.8$_b$, 75.93, 75.87, 75.7, 54.5$_{a\text{ or }b}$, 52.8$_{a\text{ or }b}$, 48.4$_c$, 31.9, 31.1, 30.3, 29.7, 29.5, 29.34, 29.25, 29.17, 29.1, 28.9, 28.3, 27.5, 23.3, 22.9, 22.84, 22.81, 22.54, 22.45, 21.15, 21.08, 14.1, 14.0, 13.9, 13.7 ppm; MS (TOF) *m*/*z* 331 ([M+Na]$^+$).
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13. For an example of a rehybridization induced by the coordination of a β oxygen atom to the metal, and the formation of a Fischer carbene complex, see Ref. 2d.
14. Procedure for the preparation of 5-chloro-6-trichloro-5,6-$d_2$-methyl-decane **2b-$d_2$**: a solution of 5-decyne (5 mL, 28 mmol), Lindlar catalyst (Pd/$CaCO_3$/PbOAc) (148 mg) and quinoline (1 mL, 8.4 mmol) in $Et_2O$ was stirred for 1.5 h at rt under a $D_2$ atmosphere (1 bar). The reaction mixture was then filtered over Celite®. The ethereal filtrate was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (*n*-hexane) afforded 5,6-$d_2$-dec-5-ene in 81% yield. Analytical data for 5,6-$d_2$-dec-5-ene: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.1–1.9 (m, 4H), 1.4–1.2 (m, 8H), 1.0–0.8 ppm (m, 6H). 5-chloro-6-trichloro-5,6-$d_2$-methyl-decane **2b-$d_2$** was then prepared according to the general procedure of Ref. 4. Analytical data for **2b-$d_2$**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.3–1.3 (m, 12H), 0.90–0.99 ppm (m, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 103.0, 64.8 (t, $J = 20$ Hz), 62.3 (t, $J = 22.5$ Hz), 32.6, 31.9, 29.3, 27.4, 22.9, 22.0,14.0, 13.8 ppm; MS (CI, $NH_3$) *m*/*z* 297 ($[M+H]^+$), 314 ($[M+NH_4]^+$).
15. 2-Butyl-2-$d_1$-3-chloro-$d_1$-methylene-1-*p*-tolyl-heptan-1-ol **4c-$d_2$** was prepared according to the procedure of Ref. 6. Analytical data for **4c-$d_2$**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ $\delta$ 7.5–7.2 (m, 4H, Ar*H*), 4.64 (br s, 1H, C*H*$OH_c$), 4.50 (br s, 1H, C*H*$OH_{a/b}$), 2.34 (s, 3H, Ar$CH_3$), 2.0–0.7 ppm (m, 22H, $CH_3$–($CH_2$)$_4$); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 142.8, 142.7, 141.8, 140.3, 140.1, 139.7, 137.7, 137.6, 137.1, 129.2, 129.1, 129.0, 127.2, 127.0, 126.3, 125.6, 115.7 (t, $J = 30$ Hz), 76.00, 75.95, 75.8, 54.0 (t, $J = 19$ Hz), 52.4 (t, $J = 20$ Hz), 48.0 (t, $J = 20$ Hz), 32.1, 31.2, 30.4, 30.04, 30.02, 29.8, 29.6, 29.5, 29.4, 29.24, 29.20, 29.0, 28.3, 27.6, 23.5, 23.04, 22.98, 22.96, 22.8, 22.7, 22.6, 21.29, 21.27, 21.2, 14.0, 13.9, 13.8; MS (TOF) *m*/*z* 333 ($[M+Na]^+$).
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