STEREOSELECTIVE ADDITION OF α-CHLORO ALLYLIC CHROMIUM
## REAGENTS TO ALDEHYDES

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Treatment of a solution of 1,1-dichloro-2-butene and benzaldehyde with $CrCl_2$ in THF-DMF at 25°C for 1 h gave threo-(Z)-4-chloro-2-methyl-1-phenyl-3-buten-1-ol in 96% yield under high stereocontrol.

Allylic metal is one of the key reagents to construct an acyclic skeleton stereoselectively.[1] We disclose here a new entry of the anion, that is an α-chloro allylic chromium reagent. The reagent is prepared by reduction of 3-alkyl-substituted 1,1-dichloro-2-propenes[2] with chromium(II) chloride in a THF-DMF mixed solvent.

In the reaction between a chloro-substituted allylic anion ($[R^2CH{=\!\!=\!\!=}CH{=\!\!=\!\!=}CHCl]^-$)[3,4] and an aldehyde ($R^1CHO$), there arise problems of regio- and two stereoselectivities, that is Z/E selectivity of a carbon-carbon double bond and threo/erythro selectivity of the newly formed vicinal stereogenic centers (Eq. 1). Fortunately, the α-chloro allylic chromium reagents were found to give nearly one isomer, threo-Z product 1a, out of the 8 candidates (1a,1b,··4a,4b) under the appropriate reaction conditions.
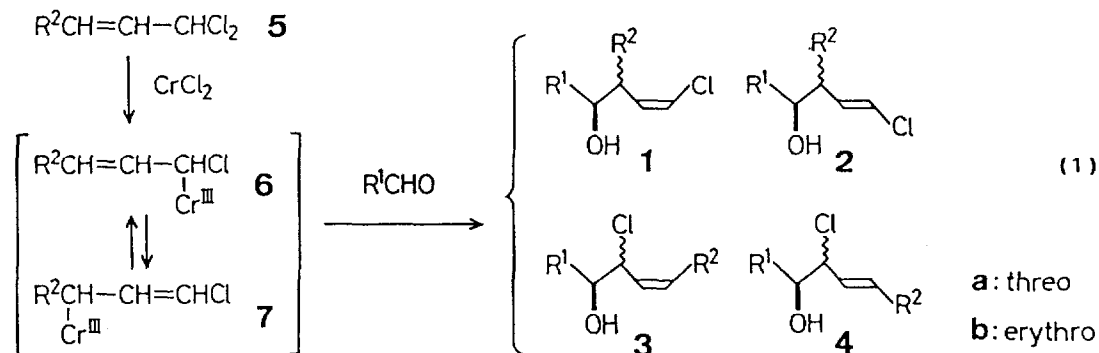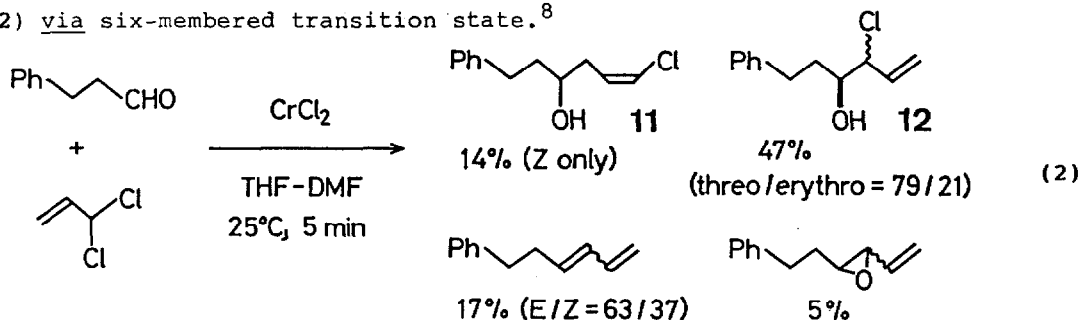

Treatment of a mixture of 3-phenylpropanal (R^1=Ph$(CH_2)_2$) and 1,1-dichloro-2-butene (5, R^2=Me) in THF-DMF (2/1) at 25°C for 1 h gave one regioisomer (1+2) having terminal alkenyl chloride[5] in 96% yield. The Z/E ratio (1/2) of the alkenyl chloride was 96/4. The threo/erythro ratio (1a/1b) of the Z product was 93/7, which was determined after dechlorination
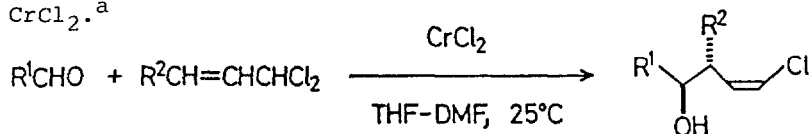
with sodium in THF at 70°C for 3 h. The yields of the desired regioisomer (1+2), the Z/E ratios (1/2), and the reaction rates depend on the solvent used. The reaction proceeded slowly (20 h) in THF and the yield and Z/E ratio of the product were not high (70% yield, 1/2=72/28). As chromium(II) salt is soluble in DMF, the reaction took place within 5 min in DMF (77% yield, 1/2=96/4). However, 7-phenyl-2,4-heptadiene was produced as a byproduct (9%). Two to one mixed solvent of THF-DMF gave the best yield and the highest selectivities. The results in Table 1 show good to excellent yields and high threo and Z selectivities of the products. Similarly to other organochromium reagents,[6] the reagent (i) gave 1,2-addition product mainly in the case of α,β-unsaturated aldehyde (run 5) and (ii) added to an aldehyde group, while a ketone group remained intact under the reaction conditions (runs 6 and 11).

Dichlorides, 3-alkyl-substituted 1,1-dichloro-2-propenes 5 were prepared by treatment of the corresponding α,β-unsaturated aldehydes with phosphorus pentachloride.[2] Crotonaldehyde was transformed into E-dichloride 8 selectively, however, (E)-2-hexenal gave two regioisomers 9 and 10. This is not a serious matter, because both isomers can be employed as precursors of the desired reagent (runs 7-11).

The effect of alkyl-substituents on 1,1-dichloro-2-propenes were examined.[7] Alkyl substituent at γ-position of dichloride is essential to get this regiochemistry. For example, reaction between a mixture of 1,1-dichloro-2-propene and 3-phenylpropanal with CrCl$_2$ in THF-DMF gave (Z)-6-chloro-1-phenyl-5-hexen-3-ol (11) in 14% yield and the major product was 4-chloro-1-phenyl-5-hexen-3-ol (12, 47%) (Eq. 2). The result suggests that the alkyl-substituent pushes away the chromium(III) to α-position of halogen to give α-chloro allylic chromium species 6 which afford the desired regioisomer (1+2) via six-membered transition state.[8]

$$
\begin{array}{c}
\text{Ph}\diagdown\diagup\text{CHO} \\
+ \\
\diagup\diagdown\diagup\text{Cl} \\
\qquad\quad\text{Cl}
\end{array}
\quad
\xrightarrow[\substack{\text{THF-DMF}\\25°\text{C, 5 min}}]{\text{CrCl}_2}
$$

Ph∕∖∕∕∖∕Cl
OH **11**
14% (Z only)

Ph∕∖∕∕ Cl
OH **12**
47%
(threo/erythro = 79/21)   (2)

Ph∕∖∕∕∕∕
17% (E/Z = 63/37)

Ph∕∖∕∕∕∕
O
5%

Reaction between 1,1-dibromo-2-butene and 3-phenylpropanal with CrCl$_2$ gave alkenyl chloride, 4-chloro-2-methyl-1-phenyl-3-buten-1-ol in 52% yield (Z/E=84/16) instead of the corresponding bromide.[9] The same halogen exchange was observed in the reaction between bromoform and aldehydes with CrCl$_2$ leading to (E)-1-halo-1-alkenes.[10]

Table 1. Reactions between 1,1-dichloro-2-propenes and aldehydes with $CrCl_2$. [a]

$$R^1CHO + R^2CH=CHCHCl_2 \xrightarrow[\text{THF-DMF, 25°C}]{CrCl_2} R^1\underset{OH}{\overset{R^2}{\diagdown}}Cl$$

Run	R^1	Dichloride (R^2)	Time h	Yield[b] %	Z/E[c]	threo/erythro[d]
1	Ph	$MeCH=CHCHCl_2$ (8)	1	96	97/3	97/3
2	$Ph(CH_2)_2-$	(Me)	2	95	96/4	93/7
3	$^nC_8H_{17}-$		1	88	95/5	99/1
4	$^cC_6H_{10}-$		1	86	97/3	>99/<1
5	$PhCH=CH-$		1	58[e]	88/12	95/5
6	$CH_3CO(CH_2)_8-$		1	85	98/2	>99/<1[f]
7	Ph	$^nC_3H_7CH=CHCHCl_2$[g] (9) $^nC_3H_7CHClCH=CHCl$ (10)	1	92	99/1	100/0
8	$Ph(CH_2)_2-$	$(^nC_3H_7)$	1	87	99/1	100/0
9	$^nC_8H_{17}-$		1	90	97/3	100/0
10	$^cC_6H_{10}-$		1	83	>99/<1	100/0
11	$CH_3CO(CH_2)_8-$		1.5	89	100/0	100/0

a) An aldehyde (1.0 mmol) was treated with a reagent prepared from a dichloride (2.0 mmol) and $CrCl_2$ (4.0 mmol) in 2:1 THF-DMF at 25°C. b) Isolated yields. c) The Z/E ratios were determined by GLPC analysis. d) The threo/erythro ratios indicated are of the corresponding Z products. The ratios were determined by GLPC analysis after dechlorination with sodium in THF at 70°C for 3 h. e) THF-dioxane 1:3 was employed as a solvent. Cinnamaldehyde was recovered (25%). f) See ref. 11. g) One to one mixture of the both dichlorides 9 and 10 was employed. See ref. 12.

General Procedure

In a reaction flask is placed $CrCl_2$ (0.49 g, 4.0 mmol) under an argon atmosphere. Tetrahydrofuran (THF, 6 mL) is added and the suspension is stirred for 15 min. Dimethylformamide (DMF, 3 mL) is added and the mixture is stirred for another 30 min. To this yellowish green suspension is added dropwise a solution of an aldehyde (1.0 mmol) and 1,1-dichloro-2-butene (0.25 g, 2.0 mmol) in THF (1.2 mL) - DMF (0.6 mL). The color of the mixture turns gradually to dark brown. After being stirred at 25°C for an appropriate time described in Table 1, the resulting mixture is poured into brine (15 mL) and extracted with ether (3x15 mL). The combined organic layers are dried ($MgSO_4$) and concentrated. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate, 5:1~10:1) affords threo-(Z)-4-chloro-2-methyl-3-buten-1-ol derivatives.[13]

References and Notes

(1) (a) R. W. Hoffmann, Angew. Chem., Int. Ed. Engl., 21, 555 (1982). (b) Y. Yamamoto and K. Maruyama, Heterocycles, 18, 357 (1982).
(2) L. J. Andrews and R. E. Kepner, J. Am. Chem. Soc., 70, 3456 (1948).

(3) (a) R. W. Hoffmann and B. Landmann, Angew. Chem., Int. Ed. Engl., 23, 437 (1984). (b) R. W. Hoffmann and S. Dresely, Angew. Chem., Int. Ed. Engl., 25, 189 (1986). (c) R. W. Hoffmann and B. Landmann, Chem. Ber., 119, 1039 (1986). (d) R. W. Hoffmann, Pure Appl. Chem., 60, 123 (1988).

(4) Recently, reaction between aldehydes and 1,3-dibromoallylchromium, derived by reduction of 1,3,3-tribromopropene with $CrCl_2$, has been reported. J. Augé, Tetrahedron Lett., 29, 6107 (1988).

(5) For the chain extension using alkenyl halides, see: (a) M. Kumada, K. Tamao, and K. Sumitani, Org. Synth., Col. Vol. 6, 407 (1988). (b) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, and H. Nozaki, J. Am. Chem. Soc., 108, 6048 (1986); H. Jin, J. Uenishi, W. J. Christ, and Y. Kishi, ibid., 108, 5644 (1986). See also ref 3c.

(6) (a) T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, Bull Chem. Soc. Jpn., 55, 561 (1982). (b) C. T. Buse and C. H. Heathcock, Tetrahedron Lett., 1978, 1685. (c) K. Takai and K. Utimoto, J. Synth. Org. Chem. Jpn., 46, 66 (1988).

(7) For the effect of alkyl-substituents on allylic chromium reagents, see: K. Takai, K. Nitta, and K. Utimoto, Tetrahedron Lett., 29, 5263 (1988).

(8) The high threo selectivity is explained by a chair-type transition state with both R^1 and R^2 at equatorial positions (A, B) as in the crotyl-chromium case.[6a,b] Hoffmann reported the reaction between α–halo allyl-boronates and aldehydes and observed the similar Z selectivity.[3] The favorable transition state A of the Cl at the axial position leading to the threo-Z isomer may be attributed to the following effects. i) Steric repulsion between the Cl and the ligand L. ii) Stereoelectronic effect, that is the transition state B having equatorial substituent Cl is not so reactive compared to A because of the decrease of the electron density by σ*(C–Cl)–π conjugation.

threo-Z (1a)   threo-E (2a)   erythro (1b, 2b)
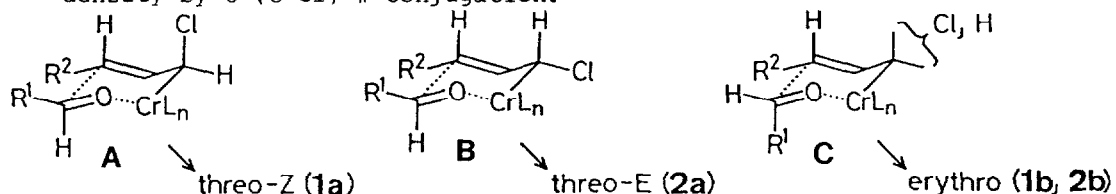
(9) The reactant, 3-phenylpropanal was remained in 31% recovery.

(10) K. Takai, K. Nitta, and K. Utimoto, J. Am. Chem. Soc., 108, 7408 (1986).

(11) Bp 140°C (bath temp, 0.6 Torr); IR (neat): 3432, 2924, 2850, 1713, 1459, 1409, 1360, 1297, 1165 cm^{-1}; NMR ($CDCl_3$): δ1.06 (d, J=7 Hz, 3H), 1.18–1.68 (m, 15H), 2.14 (s, 3H), 2.42 (t, J=7 Hz, 2H), 2.75–2.95 (m, 1H), 3.44–3.60 (m, 1H), 5.75(dd, J=7,7 Hz, 1H), 6.12 (d, J=7 Hz, 1H); MS m/e (%): 276 (M^++2, 0.4), 274 (M^+, 1.2), 186 (96), 43 (100); Found: C, 65.74; H, 10.18%. Calcd for $C_{15}H_{27}O_2Cl$: C, 65.55; H, 9.90%.

(12) NMR data of a mixture of 9 and 10 ($CDCl_3$): δ0.92 (t, J=7Hz, 3H(9)), 0.94 (t, J=7 Hz, 3H(10)), 1.38–1.59 (m, 2H(9,10)), 1.73–1.90 (m, 2H(10)), 2.01–2.15 (m, 2H(9)), 4.38 (dt, J=9,7 Hz, 1H(10)), 5.78–5.93 (m, 2H(9)), 6.01 (dd, J=9,13 Hz, 1H(10)), 6.12–6.25 (m, 1H(9)), 6.29 (d, J=13 Hz, 1H(10)).