A Practical Transformation of Aldehydes into (*E*)-Iodoalkenes with Geminal Dichromium Reagents

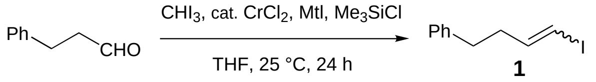
Kazuhiko Takai,* Tetsuya Ichiguchi, Shintaro Hikasa

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima, Okayama 700-8530, Japan
Fax: +81-86-251-8094; E-mail: ktakai@cc.okayama-u.ac.jp

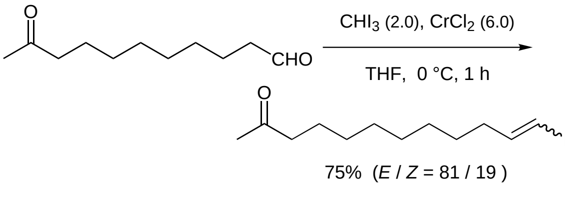
Received 17 May 1999

Abstract: A catalytic cycle of a chromium salt in a stereoselective transformation of aldehydes to (*E*)-1-iodoalkenes using a geminal dichromium reagent, is assembled with zinc, Me_3SiCl, and NaI in dioxane.

Keywords: geminal dichromium reagent, iodoform, (*E*)-1-iodoalkene, chromium(II), zinc

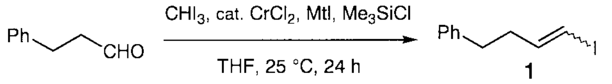


Iodoalkenes are important synthetic intermediates, especially for carbon-carbon bond formation under transition metal catalysis. One method to access the iodoalkenes is to use a geminal dichromium reagent derived from iodoform and $CrCl_2$.[1] The protocol provides (*E*)-iodoalkenes with one-carbon homologation under mild conditions in chemo- and stereoselective manners (eq. 1).[2]



Equation 1

Table 1 Product Distribution with a Variety of Metals and a Catalytic Amount of $CrCl_2$.[a]



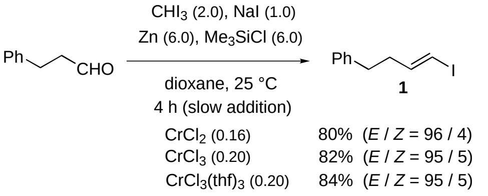
run	Mtl	equiv.	Yield / %[b]	*E* / *Z*[c]	byproducts / %
1	Mg	4.0	3	57 / 43	many products
2	Al	2.7	4	39 / 61	many products
3	Mn	4.0	17	70 / 30	$RCH=CH_2$ **2** (8), $RCH=CHSiMe_3$ **3** (3), RCHO (recov. 21)
4	Zn	4.0	46	74 / 26	$RCH=CH_2$ **2** (10), RCH=CHCl **4** (5)
5	Fe	4.0	0	--	RCHO (recov. 40)

[a]Reactions were conducted on a 1.0 mmol scale. Iodoform (2.0 mol), chromium(II) chloride (0.8 mol),[5] and Me_3SiCl (4.0 mol) were used per mole of 3-phenylpropanal (R = $Ph(CH_2)_2$). [b]Isolated yields. [c]The *E*/*Z* ratios of disubstituted olefins were determined by GLPC and/or ^1H NMR analysis.

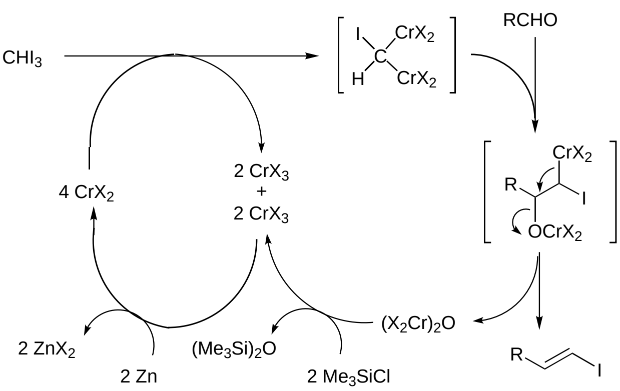
This transformation, however, requires 6-8 equiv of the one-electron reductant, $CrCl_2$ to obtain reasonable yields. In order to assemble the catalytic cycle of chromium(II) using a metal as a reductant, the reducing ability of the metal should be stronger than that of chromium(II). However, *it should be weak enough to leave the iodoform intact, or at least the reduction rate of iodoform with the metal should be considerably slower than that with chromium(II).* In 1996, Fürstner reported a chromium(II)-mediated coupling of halo olefins and aldehydes with a catalytic amount of chromium(II) using manganese as a reductant.[3,4] In the procedure, an excess amount of Me_3SiCl was employed for conversion of O-CrL_n to O-$SiMe_3$ to regenerate chromium(III) halide, which is easily reduced with the metal. Here, several metal reductants are examined to find an appropriate one that forms a catalytic cycle for the formation of iodoalkene **1** (Table 1).

Magnesium and aluminum metals are very strong and reduce iodoform to give complex mixtures (Table 1, runs 1 and 2). In contrast, a combination of zinc (4.0 equiv) and $CrCl_2$ (0.08 equiv) afforded the desired iodoalkene **1** in 46% yield (run 4). Although alkene **2** and chloroalkene **4** were produced as byproducts and the *E*/*Z* ratio was 74/26, the reaction could proceed with a catalytic amount of $CrCl_2$.

Further examination with a $CrCl_2$-zinc system revealed that the reaction completed within 1 h when 6 equiv of zinc was used; Iodoalkene **1** and chloroalkene **4** were produced in 60% (*E*/*Z* = 80 / 20) and 8%, yields, respectively. The formation of **4** could not be suppressed by addition of sodium iodide, however the yield was slightly improved.[6] The *E*/*Z* ratios of **1** depended on the solvent, and the ratio was improved to 88 / 12 in dioxane.[7] In addition, slow addition of a mixture of iodoform and an aldehyde in dioxane to a mixture of zinc, Me_3SiCl, and a catalytic amount of $CrCl_2$ in dioxane improved both the yield and the *E*/*Z* ratio markedly. Iodoalkene **1** was obtained in 80% yield (*E*/*Z* = 96 / 4) by slow addition over a period of 4 h (eq. 2).



Equation 2



Scheme 1

A plausible mechanism of the CrCl$_2$-zinc system is shown in Scheme 1. The reduction of iodoform with 4 equiv of chromium(II) gives a geminal dichromium reagent,[8] which reacts with an aldehyde followed by elimination of (X$_2$Cr)$_2$O to afford an iodoalkene. The produced (X$_2$Cr)$_2$O is converted to chromium(III) halides with Me$_3$SiCl, and the chromium(III) is then reduced with zinc to reproduce chromium(II). Two equiv. of both zinc and Me$_3$SiCl are necessary for this transformation.

Because chromium(III) is reduced with zinc to give chromium(II), the reaction proceeded using a catalytic amount of chromium(III). Both CrCl$_3$ and CrCl$_3$(thf)$_3$ could be used for the transformation (eq. 2), although the latter gave normally better yields especially in small scale experiments due to less hygroscopicity. The results with a catalytic amount of CrCl$_3$(thf)$_3$ are summarized in Table 2.

Under the standard reaction conditions (Table 1, run 1), compounds were recovered in the following order: 1-dodecene (90%); 1-dodecyne (92%); 1-chlorododecane (93%); ethyl octanoate (94%); nonanenitrile (97%). In contrast to a stoichiometric reaction with CrCl$_2$, in which nonanal diethylene acetal was recovered in 92% yield, the acetal was recovered in only 50% yield under the catalytic conditions and the acetal was converted to 1-iodododecene in 33% yield (*E* / *Z* = 90 / 10).

Typical Procedure

Procedure A: Under an argon atmosphere, Me$_3$SiCl (1.5 mL, 12 mmol) was added at 25 °C to a suspension of CrCl$_3$(thf)$_3$ (0.15 g, 0.40 mmol),[11] zinc (0.78 g, 12 mmol), and dried NaI (0.30 g, 2.0 mmol) in dioxane (20 mL). After the mixture was stirred at 25 °C for 40 min, a solution of 3-phenylpropanal (0.27 g, 2.0 mmol) and iodoform (1.6 g, 4.0 mmol) in dioxane (20 mL) was added at 25 °C to the mixture over a period of 4 h. The color of the mixture gradually turned to red during the addition. The reaction mixture was poured into water (50 mL) and organic layer was extracted with hexane (3 x 30 mL). The organic extracts were washed with aqueous Na$_2$S$_2$O$_3$ and brine, dried over anhydrous MgSO$_4$ and concentrated. Purification by column chromatography on silica gel (hexane) gave 1-iodo-4-phenyl-1-butene **1** in 84% yield (0.43 g, *E*/*Z* = 95/5) as a colorless oil along with 1-chloro-4-phenyl-1-butene (27 mg, 8%) and 4-phenyl-1-butene (5.3 mg, 2%).

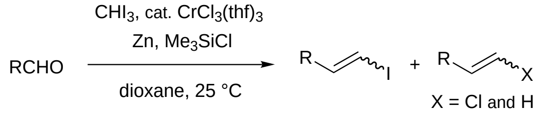
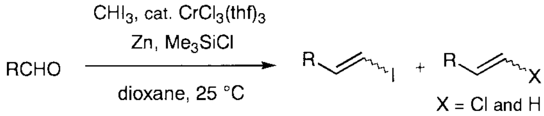
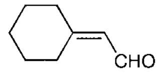


Table 2 Transformation of Aldehydes to (*E*)-Iodoalkenes.[a]



run	aldehydes	Time / h	iodide Y / %[b]	*E* / *Z*[c]	chloride Y / %	alkene Y / %
1	Ph(CH$_2$)$_2$CHO	4	84	95 / 5	8	2
2	c-C$_6$H$_{11}$CHO	5	82	97 / 3	4	0
3	PhCHO	3	78	93 / 7	6	4
4		4	71	74 / 26[d]	12	8
5	MeCO(CH$_2$)$_8$CHO	4	71	95 / 5	6	3
6	EtO$_2$C(CH$_2$)$_8$CHO	4	79	95 / 5	5	4

[a] Reactions were conducted on a 2.0 mmol scale. Iodoform (2.0 mol), chromium(III) chloride THF complex (0.20 mol),[9] zinc (6.0 mol) and Me$_3$SiCl (6.0 mol) were used per mole of aldehyde. [b] Isolated yields. [c] The *E*/*Z* ratios of disubstituted olefins were determined by GLPC and/or ^{1}H NMR analysis. [d] Ref. 10.

Procedure B: Under an argon atmosphere, Me$_3$SiCl (13 mL, 0.10 mol) was added at 25 °C to a suspension of CrCl$_3$ (0.63 g, 4.0 mmol), zinc (5.9 g, 90 mmol), and dried NaI (3.0 g, 20 mmol) in dioxane (100 mL). After the mixture was stirred at 25 °C for 40 min, a solution of 3-phenylpropanal (2.7 g, 20 mmol) and iodoform (12 g, 30 mmol) in dioxane (50 mL) was added at 25 °C (water bath) to the mixture over a period of 12 h. The reaction mixture was poured into water (200 mL) and organic layer was extracted with hexane (3 8x 100 mL). The organic extracts were washed with Na$_2$SO$_4$ and brine, dried over anhydrous MgSO$_4$ and concentrated. Distillation of the crude product gave 1-iodo-4-phenyl-1-butene **1** in 70% yield (3.6 g, *E*/*Z* = 94/6) as a colorless oil along with 1-chloro-4-phenyl-1-butene (0.20 g, 6%) and 4-phenyl-1-butene (30 mg, 1%).

Acknowledgement

We thank Dr. Alois Fürstner of the Max-Planck-Institut für Kohlenforschung for useful suggestions. Financial support by a Grant-in-Aid for Scientific Research on Priority Area No. 283 from the Ministry of Education, Science, Sports and Culture of Japan is gratefully acknowledged

References and Notes

(1) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(2) For some representative application to total synthesis, see: Nicolaou, K. C.; Bertinato, P.; Piscopio, A. D.; Chakraborty, T. K.; Minowa, N. *J. Chem. Soc., Chem. Commun.* **1993**, 619. Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451. Kende, A. S.; Koch, K.; Dorey, G.; Kaldor, I.; Liu, K. *J. Am. Chem. Soc.* **1993**, *115*, 9842. See also ref. 7.

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(5) Chromium(II) chloride (99.9% purity) was purchased from Aldrich Chemical Co. Zinc powder (99.9% purity) was purchased from Merck Co. and activated by washing with 1M hydrochloric acid, water, methanol, and ether, and dried in vacuo.

(6) Sodium iodide was dried at 120 °C (2 Torr) for 1 day. Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874. Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *Synthesis* **1979**, 61. See also, ref. 4.

(7) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. In contrast to the stoichiometric reaction in dioxane where the reaction did not complete after 4 days, the catalytic process completed within 4 h in the solvent.

(8) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951; Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 1443; Takai, K.; Shinomiya, N.; Kaihara, H.; Yoshida, N.; Moriwake, T.; Utimoto, K. *Synlett* **1995**, 963.

(9) Chromium(III) hexahydrate (99.995% purity) was purchased from Aldrich Chemical Co. and dehydrated by treatment with thionyl chloride. Pray, A. R. *Inorg. Synth.* **1954**, *5*, 153. Chromium(III) chloride THF complex (97% purity) was purchased from Aldrich Chemical Co.

(10) Similar low geometrical selectivity of the produced olefin was observed in iodomethylenation of cyclohexylideneacetaldehyde with the reagent derived from CHI_3 and a stoichiometric amount of $CrCl_2$.[1]

Article Identifier:
1437-2096,E;1999,0,08,1268,1270,ftx,en;Y11399ST.pdf