A Multicomponent Redox System Accounts for the First Nozaki−Hiyama−Kishi Reactions Catalytic in Chromium

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Scheme 1

R^1 = allyl, alkenyl, alkynyl, aryl, propargyl

Scheme 2

The addition of organochromium compounds to aldehydes originally described by Nozaki and Hiyama et al. has evolved into a very powerful method for C−C bond formation (Scheme 1).[1,2] This transformation is highly chemoselective and displays an exceptional compatibility with an array of functional groups in both reaction partners. The nucleophiles are readily available by oxidative insertion of Cr(2+) into a wide range of (functionalized) substrates such as allyl, propargyl, aryl, or alkenyl halides, alkenyl triflates, allyl phosphates etc.[3] Kishi's finding that nickel salts exhibit a catalytic effect on the formation of the C−Cr bond has greatly improved the reliability of this process,[4] which has ever since been frequently used as the key step in most impressive total syntheses of natural products of utmost complexity.[5,6]

Two major drawbacks, however, are pending. First, stereochemical control over the newly formed chiral center in Nozaki−Hiyama−Kishi reactions is still in its infancy.[7] Second, as Cr(2+) is a one-electron donor, 2 mol of this reducing agent per mol of halide are required to form the organochromium intermediate; in practice, a huge excess (usually 200−1600 mol %) is mandatory. The toxicity of chromium (and nickel) salts, however, obviously makes this versatile process inadequate for applications to pharmaceutical chemistry as well as for any large-scale synthesis. Herein we address this latter shortcoming and report the first examples of Nozaki−Hiyama−Kishi reactions catalytic in chromium.

Our approach relies on the following concept: CrCl$_2$ can be prepared by reduction of CrCl$_3$ with different reducing agents.[1,8] The low-valent salt inserts into the C−X bond of the substrate with formation of 1 mol of CrX$_3$ and the organochromium nucleophile **A**, which then reacts with the aldehyde giving rise to a chromium alkoxide **B**. The high stability of the O−Cr-(3+) bond formed drives the conversion but makes catalysis a difficult task. Nevertheless **B** might react with a chlorosilane in view of the pronounced oxophilicity of silicon. Since this would lead to the O-silylated product **C** and regenerate the second mole of CrX$_3$, a catalytic cycle might emerge (Scheme 2).

The stoichiometric reducing agent chosen must efficiently reduce CrX$_3$ but has to be inert toward the reducible substrates; moreover, its salts should be significantly less toxic than those of chromium. Our endeavors in low-valent titanium chemistry suggested the use of the combination of Zn dust and TMSCl for such a purpose.[9] Although some turnovers could be reached, this particular combination turned out to be impractical. Enolizable aldehydes gave poor results since they were partly transformed into the corresponding silyl enol ethers (Table 1, entry 3) due to the Lewis acidity of the zinc halides accumulating during the course of the reaction.

A likely substitute for zinc is manganese: it is very cheap and exhibits an appropriate reduction potential,[10] and its salts are nontoxic and rather weak Lewis acids. Moreover commercial manganese powder does not insert into C−X bonds except for very reactive allylic halides.[11] This was confirmed by a series of control experiments with iodobenzene and octanal as the substrates (Table 1); with either Mn/chlorosilane or Mn/chlorosilane/NiCl$_2$ cat. no product was formed (GC yield <3%). In contrast, a combination of *catalytic amounts of CrCl$_2$ (≈15 mol %, doped with NiCl$_2$)*, Mn powder, and a chlorosilane cleanly converted these substrates into a mixture of **1a** and its silyl ether **1b**.[12] A workup with aqueous Bu$_4$NF gave alcohol

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(2) Reviews: (a) Saccomano, N. A. In *Comprehesive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 173−209. (b) Cintas, P. *Synthesis* **1992,** 248−257. (c) Hodgson, D. M. *J. Organomet. Chem.* **1994,** *476,* 1−5.

(3) For the use of substrates other than halides, see the following. (a) Alkenyltriflates: Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986,** *108,* 6048−6050. (b) Allylic phosphates: Nowotny, S.; Tucker, C. E.; Jubert, C.; Knochel, P. *J. Org. Chem.* **1995,** *60,* 2762−2772.
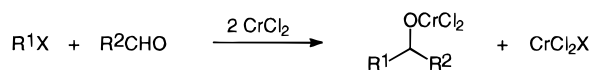
(4) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986,** *108,* 5644−5646. (b) Kishi, Y. *Pure Appl. Chem.* **1992,** *64,* 343−350. This nickel effect has been independently reported by Nozaki et al., *cf.* ref 3a.

(5) Stereoselective reactions of crotylchromium species have received particular attention, *cf.*: (a) Mulzer, J.; Kattner, L.; Strecker, A. R.; Schröder, C.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991,** *113,* 4218−4229. (b) Jubert, C.; Nowotny, S.; Kornemann, D.; Antes, I.; Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1992,** *57,* 6384−6386. (c) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988,** 5263−5266. (d) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978,** 1685−1688. (e) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982,** 2343−2346.

(6) See: (a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X. Y. *J. Am. Chem. Soc.* **1995,** *117,* 1171−1172. (b) Kishi, Y. *Chemtracts: Org. Chem.* **1988,** *1,* 253−265. (c) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992,** *114,* 3162−3164. (d) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989,** *111,* 2735−2737. (e) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988,** *110,* 5198−5200. (f) Chen, S. H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991,** *56,* 5834−5845. (g) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995,** *117,* 6224−6233. (h) Lu, Y. F.; Hartwig, C. W.; Fallis, A. G. *J. Org. Chem.* **1993,** *58,* 4202−4204. (i) Still, C. W.; Mobilio, D. *J. Org. Chem.* **1983,** *48,* 4785−4786. (j) Eckhardt, M.; Brückner, R.; Suffert, J. *Tetrahedron Lett.* **1995,** 5167−5170. (k) Dancy, I.; Skrydstrup, T.; Crévisy, C.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1995,** 799−800. (l) Brandstetter, T.; Maier, M. E. *Tetrahedron* **1994,** *50,* 1435−1448. (m) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993,** *58,* 165−169. (n) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995,** *117,* 10391−10392.
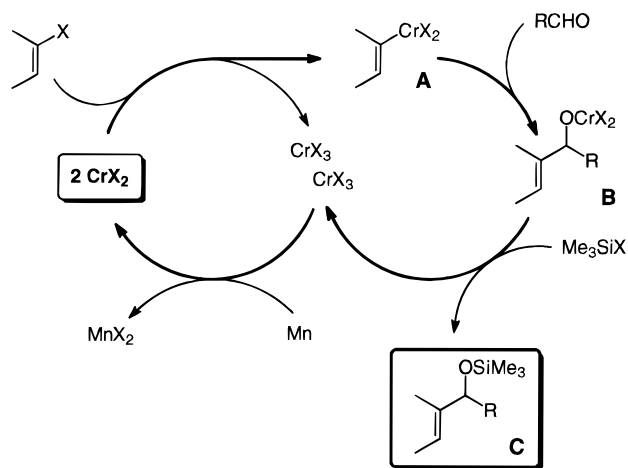
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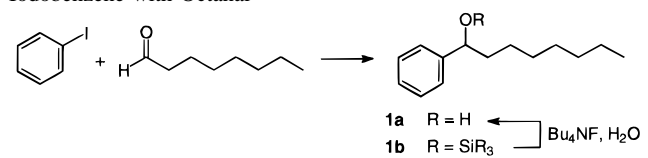
(9) The combination of TiCl$_3$ cat., Zn, and R$_3$SiCl accounts for the first carbonyl coupling reactions catalytic in titanium, *cf.*: Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995,** *117,* 4468−4475.

(10) Electrochemical redox potentials: Cr^{3+} + e$^-$ ⇌ Cr^{2+} (−0.41 V); Zn^{2+} + 2e$^-$ ⇌ Zn (−0.76 V); Mn^{2+} + 2e$^-$ ⇌ Mn (−1.03 V). *Handbook of Chemistry and Physics,* 62nd ed.; CRC Press: Boca Raton, FL, 1982.

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(12) Complete silylation could not be reached. This seems to be a limiting factor for the number of turnovers.

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Table 1. Control Experiments for Cr(2+)-Mediated Reaction of Iodobenzene with Octanal

entry	CrCl$_2$ (mol %)[a]	additives	T (°C)	isolated yield (%)[b]
1	400		20	78[c]
2	400		50	65
3	30	Zn, TMSCl	70	30−40[d]
4	15	Mn, TMSCl	50	67
5	15	Mn, ClMe$_2$Si(CH$_2$)$_3$CN	50	72
6	9	Mn, ClMe$_2$Si(CH$_2$)$_3$CN	50	58
7	0	Mn, ClMe$_2$Si(CH$_2$)$_3$CN	50	0[e]
8	0	Mn, ClMe$_2$Si(CH$_2$)$_3$CN, NiCl$_2$ (cat.)	50	0[e]

[a] Unless stated otherwise the reactions were carried out in DME/DMF (20/3) using CrCl$_2$ doped with NiCl$_2$ (≈15%). [b] After desilylation of the admixed **1b**. [c] In pure DMF as solvent. [d] Formation of 1-(trimethylsilyloxy)-1-octene as side reaction, see text. [e] GC yield <3%.

1a in 67−72% yield, which favorably compares to the 65−78% obtained under conventional conditions using 400 mol % of CrCl$_2$ as the reagent.

The experimental parameters of the catalytic process have been carefully optmized. Reactions of aryl and alkenyl halides (triflates) proceed properly with ≈15 mol % CrCl$_2$, while allylic halides require only ≈7 mol % of this catalyst. Except for allylic substrates, the reactions were carried out at 50 °C (±3 deg) in DME/DMF (20/3)[13] since the conversion was too slow at lower temperatures. The addition of catalytic amounts of LiI to TMSCl as well as replacing TMSCl by TMSBr, (EtO)$_3$SiCl, ClMe$_2$SiCH$_2$CH$_2$SiMe$_2$Cl, or ClMe$_2$Si(CH$_2$)$_3$CN (*cf.* Table 2) did not significantly improve the yields.

The catalytic procedure nicely applies to a set of representative Nozaki−Hiyama type reactions.[14] As can be seen from Table 2, iodobenzene reacts smoothly with aromatic as well as with different aliphatic aldehydes. Entry 4 highlights the chemoselectivity of this process; thus, Cr(2+) exclusively inserts into the aryl iodide while the alkyl chloride group of 6-chlorohexanal is compatible. Aryl halides containing either potential donor sites or reducible functional groups such as 2-iodothiophene or ethyl 4-iodobenzoate can also be used. Alkenyl iodides and, in particular, alkenyltriflates[3a] turned out to react smoothly to the corresponding allylic alcohols. However, we noticed some influence of the electronic properties of the chosen aldehyde on the reaction path; aliphatic aldehydes, benzaldehyde, and analogues bearing electron-donating substituents reacted properly, while methyl 4-formylbenzoate as the electrophile gave the corresponding pinacol as the major product (Scheme 3). In this case the ester group obviously facilitates a single-electron transfer from Cr(2+) to the aldehyde function, with formation and subsequent dimerization of the ketyl radical anion. This observation is in good accordance with the experience gained with other pinacolization methods.[15] Allylic bromides were found to react particularly well in THF at ambient temperature rather than at 50 °C, requiring only ≈7 mol % CrCl$_2$ which must not be doped with NiCl$_2$ in order to prevent Wurtz-coupling.[16]

In summary, we have described the first Nozaki−Hiyama−Kishi reactions using catalytic amounts of CrCl$_2$ (7−15 mol

Table 2. Nozaki−Hiyama−Kishi Reactions Catalytic in Chromium[a]

entry	RX	aldehyde	product	ClMe$_2$Si(CH$_2$)$_3$CN yield (%)[b]	Me$_3$SiCl yield (%)[b]
1	PhI	PhCHO		88	62
2	PhI	CH$_3$(CH$_2$)$_6$CHO		72	67
3	PhI	C$_6$H$_{11}$CHO		71	
4	PhI	Cl(CH$_2$)$_5$CHO		64[c]	66
5	(2-thienyl-I)	CH$_3$(CH$_2$)$_6$CHO		57	
6	EtOOC-C$_6$H$_4$-I	PhCHO			57[d]
7	(enol triflate)	CH$_3$(CH$_2$)$_6$CHO			61
8	(enol triflate)	MeO-C$_6$H$_4$-CHO			76
9	(vinyl iodide)	MeO-C$_6$H$_4$-CHO			75
10	(enol triflate)	(piperonal)			80
11	allyl-Br	CH$_3$(CH$_2$)$_6$CHO			78[e]
12	Br-acrylate OEt	PhCH$_2$CH$_2$CHO			72[e,f]

[a] Unless stated otherwise, all reactions were carried out with CrCl$_2$ (15 mol %, doped with cat. NiCl$_2$), Mn powder (4.2 mmol), aldehyde (2.5 mmol), RX (5 mmol), and chlorosilane (6 mmol) in DMF/DME (20/3) at 50 °C. [b] Refers to the product obtained after desilylation (aqueous Bu$_4$NF) of the crude mixture. [c] Isolated after acetylation of the crude product. [d] 4,4′-Bis(ethoxycarbonyl)diphenyl as byproduct (20% based on I-C$_6$H$_4$-COOEt). [e] The reaction was performed with undoped CrCl$_2$ (7 mol %) at ambient temperature in THF. [f] The α-methylene-γ-lactone was cyclized upon treatment of the crude product with catalytic amounts of *p*-TsOH·H$_2$O.

Scheme 3
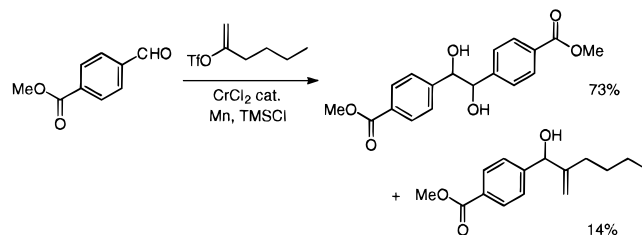
%), which is constantly recycled by the relatively nontoxic manganese. The limiting factor for the number of turnovers seems to be the incomplete σ-bond metathesis between the chromium alkoxide initially formed and the chlorosilane additive.[12] We are now intensively working to refine this crucial step in order to further reduce the quantity of toxic Cr(2+) and to further explore the full scope of the new procedure.

(13) Pure DMF, although superior in the stoichiometric reaction (Table 1, entry 1), gave inferior yields. The CrCl$_2$ should be colorless; pale-green batches result in lower yields.

(14) A representative procedure is described in the supporting information.

(15) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729−1734 and literature cited therein.

(16) One might envisage that allylic halides react with Mn without any assistance of Cr(2+) (*cf.* ref 11). Control experiments, however, showed that under the conditions employed the combination Mn/TMSCl without CrCl$_2$ catalyst leads to very poor conversion (19% in GC after 90 h reaction time!).