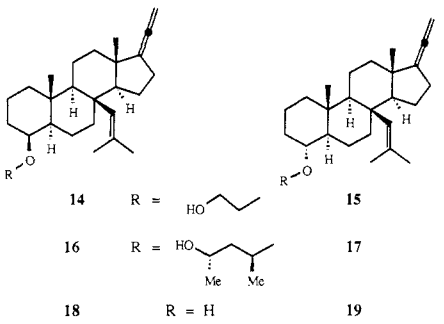
di-*tert*-butylpyridine for 1 h at −5 °C, followed by quenching with methanol, then ether, and dilute HCl, gave after flash chromatography two major components representing a 45% yield of the C-4 axial isomer **14** and 22% of the equatorial epimer **15**. The structures and relative configurations of these *racemic* materials were established unequivocally by X-ray analysis of the purified crystals, mp 142–144 °C (compound **14**) and 145–146 °C (compound **15**). Several byproducts, e.g., the TMS ethers of **14** and **15**, were isolated from the reaction mixture, raising the total yield of all-trans ring-fused products to 76%.



The 6:5 mixed catalyst used above for the cyclization of acetal **13** was too mild for the less reactive chiral acetal **12**, which, after several exploratory experiments using racemic material, was cyclized as follows. To a solution of acetal **12** (39 mg, 0.076 mmol), 2,6-di-*tert*-butylpyridine (0.038 mmol), and tetracosane (1.3 mg as a GC internal standard) in pentane (6.6 mL) at −45 °C was added a freshly prepared (see above) solution of $TiCl_4$ (0.23 mmol) and $Ti(OiPr)_4$ (0.076 mmol) over a 15-min period via a motorized syringe. After an additional 20 min at −45 °C, methanol (300 μL) and triethylamine (50 μL) were added, and the mixture was worked up with ether and dilute HCl. The ratio of axial to equatorial product was estimated to be 9:1 by GC. Filtration through a short column of silica gel gave 34.5 mg of crude axial isomer **16** (purity 70% by GC). The chiral auxiliary was removed from this crude product via the established procedure[4a] involving oxidation to the ketone followed by β-elimination. Thus, after purification by flash chromatography, a 61% yield (overall from acetal **12**) of axial **18** and 2.4% of equatorial product **19** were obtained. Further purification by reverse-phase HPLC (10% ether in CH_3CN) gave pure **18** (42% yield), $[\alpha]^{23}_D$ −13.6° (c = 0.0062 g/mL, CCl_4). The optical purity of this material was determined, as in the model series,[4a] by GC analysis (base-line separation) of the Mosher esters to be 90% ee. The relative configuration of this product follows from the unequivocally established constitution of product **14** (X-ray analysis, see above). That the absolute configuration is that of the natural steroids (formula **18**) is assured by the established stereochemical course of the cyclization of **3**[4] as well as of many related reactions of chiral acetals.[3] It also follows from prior art[9] that the minor equatorial isomer has the antipodal steroid configuration *enantio*-**19**.

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Supplementary Material Available: Characterization data, including IR and NMR spectra as well as C, H analyses, for new compounds as well as ORTEP plots for substances **14** and **15** (8 pages). Ordering information is given on any current masthead page.

(9) See ref 4 and citations therein.

Preparation of Alkylchromium Reagents by Reduction of Alkyl Halides with Chromium(II) Chloride under Cobalt Catalysis

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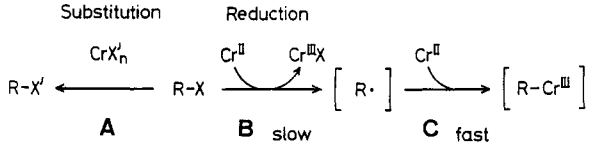
Summary: Alkyl halides and tosylates are reduced with $CrCl_2$ in the presence of a catalytic amount of vitamin B_{12} or cobalt phthalocyanine to give alkylchromium reagents, which add to aldehydes without affecting the coexisting ketone or ester groups.

Sir: Notwithstanding the widespread utility of traditional organometallic reagents such as RLi and RMgX, certain limitations in their use have yet to be satisfactorily addressed. As a consequence of their high basicity and nucleophilicity, these compounds tolerate only a small number of functional groups, making it difficult to discriminate effectively between the different acceptor sites on a polyfunctional substrate molecule. Organotitanium,[1] -chromium,[2] -zinc,[3] -copper,[4] and -lead[5] reagents have provided a solution to the difficulty. Organotitanium, -copper, and -lead reagents are usually prepared through transmetalation from RLi or RMgX. Compared to the transmetalation methods, however, direct preparation through the reduction of organic halides with low-valent metals has some advantages. For instance, reagents with functional groups subject to nucleophilic attack such as ketones, esters, and nitriles could be prepared without the need for prior protection of these groups. Thus we undertook the preparation of various alkylchromium reagents, through

Scheme I



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(2) For a review, see: Takai, K.; Utimoto, K. *J. Synth. Org. Chem., Jpn.* **1988**, *46*, 66.

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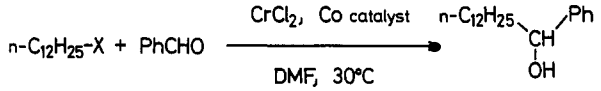
Table I. Grignard-Type Addition between 1-Haloalkanes and Benzaldehyde[a]



	VB_{12}		CoPc	
X	time/h	yield/%[b]	time/h	yield/%[b]
I	5	89	3	91
Br	5	95	10	75
Cl	16	45	16	<1[c]
	24	72[d]		
[OTs]	24	74[d]	24	<1[e]

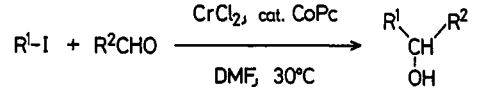
[a] A mixture of benzaldehyde (1.0 mmol) and 1-haloalkane (2.0 mmol) was treated at 30 °C with $CrCl_2$ (4.0 mmol) in the presence of vitamin B_{12} (0.04 mmol) or cobalt phthalocyanine (0.2 mmol) in DMF. [b] Isolated yields. [c] Recovery of unreacted 1-chlorododecane: 83%. [d] The amount of vitamin B_{12} was increased to 0.2 mmol. [e] Unreacted dodecyl tosylate was recovered in 16% yield, and the rest was transformed into 1-chlorododecane in 83% yield. Benzaldehyde was recovered in 79% yield.

the reduction of alkyl halides with chromium(II) salts.

Chromium(II) salts readily reduce the more reactive halides,[6] such as allylic[7] and alkynyl compounds.[8] It is more difficult, however, to reduce simple alkyl halides to afford alkylchromium reagents[9] in aprotic solvents.[10,11] Treatment of a mixture of 1-iodododecane and benzaldehyde with $CrCl_2$ in DMF (dimethylformamide) at 30 °C for 16 h afforded only 7% of the desired adduct, 1-phenyl-1-tridecanol, and most of the halide was recovered as 1-chlorododecane (88%) in our hands.[12] This result suggests that the rate of substitution by chloride ion (step A in Scheme I) is faster than that of reduction with chromium(II) ion (step B).[13] It is known that reduction of alkyl radicals by Cr(II), leading to alkyl–Cr(III) species (step C), is a rapid process.[14] Thus we tried to facilitate the formation of alkyl radicals from alkyl halides (step B) by adding various transition-metal catalysts.

Among those examined, vitamin B_{12} (VB_{12})[15] and cobalt phthalocyanine (CoPc)[16] in particular were found to be effective for the Grignard-type reaction (Table I). The reactivity of the haloalkanes decreased in the order I > Br > Cl ~ OTs.[16b] There are notable differences between the two catalysts: Iodo, bromo, chloro, and tosyloxy compounds were reduced to give the alkylchromium reagents with $CrCl_2$ under vitamin B_{12} catalysis, while the latter two compounds remained in the presence of CoPc.[17]

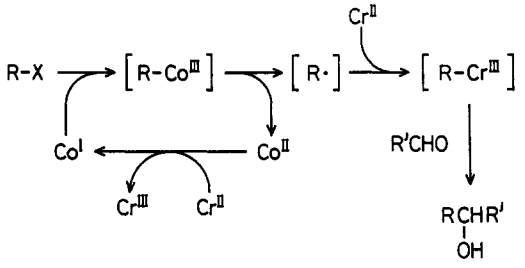
Table II. Grignard-Type Addition between 1-Iodoalkanes and Aldehydes[a]



run	R^1	R^2	time/h	yield/%[b]
1	n-$C_{12}H_{25}$-	Ph	2.5	91
2		n-C_8H_{17}-	6	89
3		c-C_6H_{11}-	10	75
4		PhCH=CH-	3.5	50
5		$MeCO(CH_2)_8$-	10	86
6	$MeCO(CH_2)_5$-	Ph	5	89
7		n-C_8H_{17}-	10	73
8	$EtOOC(CH_2)_5$-	Ph	5	91
9		n-C_8H_{17}-	11	80
10	[$EtOOC(CH_2)_5OTs$]	Ph	24[c]	85
11		n-C_8H_{17}-	24[c,d]	74
12	$Cl(CH_2)_{12}$-	Ph	3.5	85
13	i-Bu		10	64[e]
14		n-C_8H_{17}-	15	38[e]
15	c-$C_{12}H_{23}$-	Ph	20	2[f]

[a] The aldehyde (1.0 mmol) was treated at 30 °C with a reagent prepared from 1-iodoalkane (2.0 mmol), $CrCl_2$ (4.0 mmol), and a catalytic amount of CoPc (0.2 mmol) in DMF.[17] [b] Isolated yields. [c] Ethyl 6-(tosyloxy)hexanoate (2.0 mmol) and a catalytic amount of vitamin B_{12} (0.1 mmol) were employed instead of the corresponding iodide (2.0 mmol) and CoPc (0.2 mmol), respectively. [d] Nonanal (1.0 mmol) was treated at 30 °C with a reagent prepared from the tosylate (4.0 mmol), $CrCl_2$ (8.0 mmol), and vitamin B_{12} (0.2 mmol). [e] The amount of reactant aldehyde was reduced to 0.67 mmol. [f] Cyclododecene (54%) and cyclododecane (21%) were produced as major products.

Scheme II



Co: Vitamin B_{12} (VB_{12}) or Cobalt(II)phthalocyanine (CoPc)

The results are summarized in Table II. In the case of α,β-unsaturated aldehyde, the 1,2-adduct was the principle product, as with other organochromium reagents (run 4).[2] Reduction of alkyl halides to the corresponding chromium reagents under mild condition enables the Grignard-type reaction to take place without prior protection of ketone and ester groups (runs 5–11). The cobalt-catalyzed reaction exhibited the following limitations: (i) Reaction between iodocyclododecane and benzaldehyde resulted in the

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(10) Kochi, J. K.; Mocadlo, P. E. *J. Am. Chem. Soc.* **1966**, *88*, 4094.
(11) Alkylchromium reagents with α-thio groups can be prepared without transition-metal catalysts. Nakatsukasa, S.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5045.
(12) Treatment of 1-chlorododecane under the same reaction conditions resulted in 97% recovery of the unchanged chloride.
(13) Similar halogen exchange is observed in the reaction between bromoform and aldehydes with $CrCl_2$ in THF. See: Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
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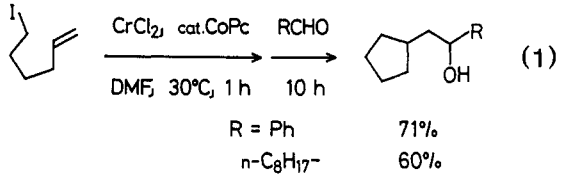
(17) A solution of an iodoalkane (2.0 mmol) and an aldehyde (1.0 mmol) in DMF (2 mL) is added at 30 °C to a stirring dark blue suspension of $CrCl_2$ (0.49 g, 4.0 mmol) and CoPc (0.11 g, 0.20 mmol) in DMF (10 mL). After having stirred at 30 °C for an appropriate length of time (Table II), the mixture is filtered through Hyfro-Super Cel, and the residue is washed with ether (10 mL). The filtrate is poured into brine (20 mL) and extracted with ether (2 × 15 mL). The combined extracts are dried (Na_2SO_4) and concentrated. The crude product is purified by short-column chromatography on silica gel. In the case of chloroalkane and alkyl tosylate, vitamin B_{12} (54 mg, 0.04 mmol) is employed instead of the CoPc.

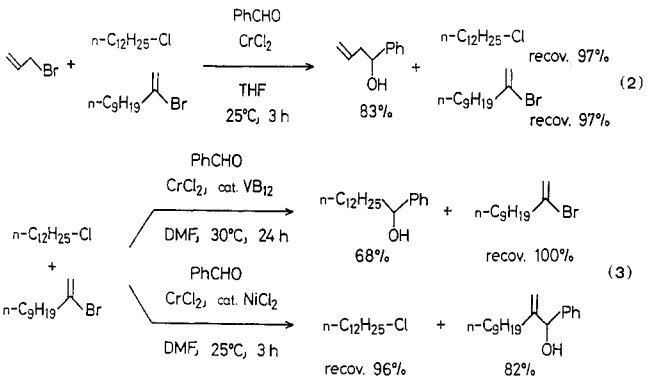
formation of cyclododecene (E/Z mixture) and cyclododecane, while the aldehyde remained unchanged (run 15). (ii) Reaction with isobutyl iodide proceeded more slowly than that with n-alkyl iodide, and the yields were rather low when compared to those with n-alkyl iodides. These drawbacks stem mainly from the steric hindrance of the alkylchromium and from the thermal stabilities of the chromium–carbon σ-bond, which decrease in the sequence normal > secondary > tertiary[18] and Me > Et > n-Pr > i-Bu.[9b]

A possible mechanism for the formation of alkylchromium reagents under cobalt catalysis follows (Scheme II): (i) reduction of Co(III) or Co(II) into Co(I) by Cr(II); (ii) oxidative addition of an alkyl halide to Co(I); (iii) homolytic cleavage of the C–Co(III) bond to yield an alkyl radical and Co(II) (vide infra);[20] (iv) reductive trapping of the alkyl radical by Cr(II) to generate the alkylchromium species, which then couples with an aldehyde; (v) regeneration and recycling of Co(I) from Co(II) by Cr(II).

When 6-iodo-1-hexene was permitted to react with aldehydes, the major products were cyclized adducts (eq 1).[21,22] This result suggests the possibility of termination of the radical cyclization by intermolecular trapping with a species such as an alkyl anion.[23]



The chemoselective preparation of organochromium reagents was achieved by changing either the catalyst or the solvent (eq 2 and 3). Alkenyl and alkyl halides remained unchanged under the conditions of the preparation of allylchromium reagents; on the other hand, alkenyl- and alkylchromium reagents were produced selectively under nickel[24] and cobalt catalysis, respectively.



Acknowledgment. Financial support from the Ministry of Education, Science, and Culture of Japan (Grant-in Aid No. 63607518) is acknowledged.

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(20) Direct transmetalation from cobalt to chromium is reported. Espenson, J. H.; Shveima, J. S. *J. Am. Chem. Soc.* **1973**, *95*, 4468. Espenson, J. H.; Sellers, T. D., Jr. *Ibid.* **1974**, *96*, 94.
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New Method for the Synthesis of Boron-10 Containing Nucleoside Derivatives for Neutron-Capture Therapy via Palladium-Catalyzed Reaction

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Summary: The palladium-catalyzed coupling reaction of halogenated nucleoside derivatives with the aryltin compound having a boronic moiety proceeded chemoselectively at the C–Sn bond rather than the C–B bond to give boron-containing nucleoside derivatives for neutron-capture therapy in good yields.

Sir: The theoretical attractiveness of neutron capture therapy (NCT) versus other radio- and chemotherapic approaches for the treatment of cancer is as appealing now as when first proposed by Locher.[1] The interaction of boron-10 and thermal neutron, each relatively innocuous, produces intense, ionizing radiation that is confined to single or adjacent cancer cells as shown in eq 1.

$$^{10}B + {}^{1}n \rightarrow {}^{7}Li + {}^{4}He + 2.4\ MeV \qquad (1)$$

Since a practical method for production of highly purified thermal neutron has been achieved recently,[2] much attention has been paid to the design and synthesis of boron-10 (^{10}B) carriers that deliver adequate concentration of ^{10}B atoms to tumors.[3] To significantly increase physiological selectivity for tumors, several third-generation compounds such as ^{10}B-containing acetylcholine,[4] nucleosides,[5,6] and amino acids[7-9] have been synthesized in recent years. However, new systematic synthetic methods are still

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