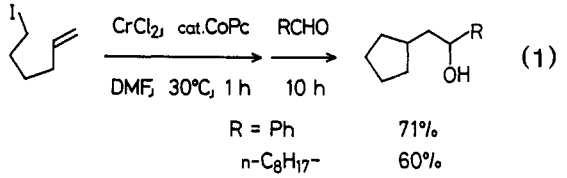
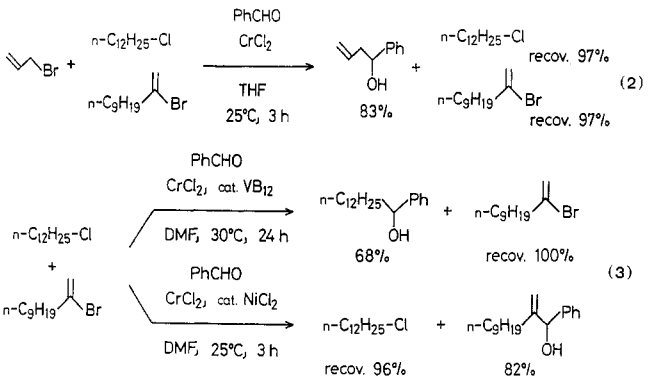
formation of cyclododecene (E/Z mixture) and cyclododecane, while the aldehyde remained unchanged (run 15). (ii) Reaction with isobutyl iodide proceeded more slowly than that with n-alkyl iodide, and the yields were rather low when compared to those with n-alkyl iodides. These drawbacks stem mainly from 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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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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(2) (a) Kobayashi, T.; Kanda, K. *Radiat. Res.* **1982**, *91*, 77. (b) Kobayashi, T.; Kanda, K. *Nucl. Instrum. Methods* **1983**, *204*, 525.
(3) (a) Yamamoto, Y. *Kagaku* **1986**, *41*, 774. (b) Soloway, A. H. *Prog. Boron Chem.* **1964**, *1*, 203.
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(6) Schinazi, R. F.; Prusoff, W. H. *J. Org. Chem.* **1985**, *50*, 841.
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(8) Matteson, D. S.; Sadhu, K. M.; Leinhard, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 5241.
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Scheme I

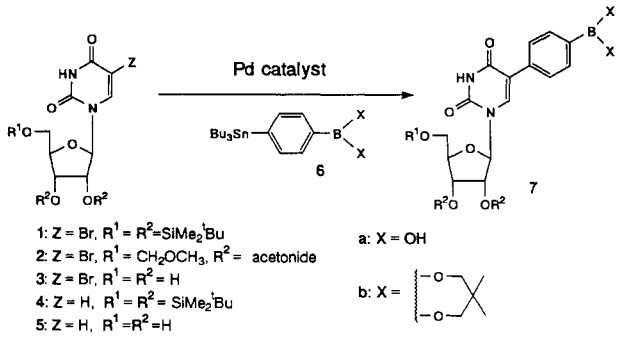


Table I. Reaction of 6 with 1–3 in the Presence of Pd Catalysts

entry	halide	aryltin	catalyst	solvent	yield of 7, %
1	1	**6a**	$Pd(PPh_3)_4$	toluene	0[a]
2	1	**6b**	$Pd(PPh_3)_4$	toluene	79[b]
3	1	**6b**	$PdCl_2(PBu_3)_2$	toluene	9[b,c]
4	1	**6b**	$PdCl_2COD$	toluene	0[c]
5	1	**6b**	$Pd(PPh_3)_4$	tetrahydrofuran	0[c]
6	1	**6b**	$Pd(PPh_3)_4$	*N,N*-dimethylformamide	0[c]
7	2	**6b**	$Pd(PPh_3)_4$	toluene	20[c]
8	3	**6b**	$Pd(P.Ph_3)_4$	ethanol	0[c]

[a] The dehalogenation product **5** was obtained in 30% yield. [b] The dehalogenation product **4** was obtained as a byproduct; 10% yield in entry 2 and 20% yield in entry 3. [c] Stoichiometric amounts of the starting material were recovered.

required for further development of this therapy to elucidate the relation between activity to ^{10}B NCT and molecular structure. Nevertheless, recent interest in organoboron chemistry has been directed primarily to use boron compounds as a synthetic tool.[10]

For the present purpose, the carbon–boron bond has to be kept stable in the final target molecule. One of the most often used procedures for preparation of ^{10}B carriers is the direct reaction of the carbanions (Y^-Li^+) with trialkyl borates[6] (eq 2). However, the desired coupling does not

$$Y^-Li^+ + B(OR)_3 \rightarrow Y\text{-}B(OR)_2 \quad (2)$$

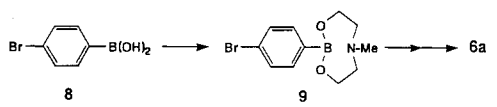
take place in certain cases, since the nucleophilicity of certain carbanions is not strong enough[11] or the carbon–boron bond of the product is not stable enough to be isolated.[12]

In this communication, we report a new general synthetic method for ^{10}B-containing nucleoside derivatives by using palladium-catalyzed coupling reaction of halogenated nucleosides with aryltin compounds having a boronic moiety (eq 3).

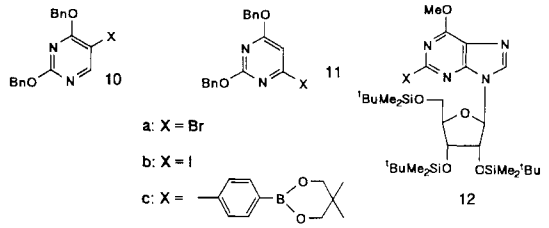
$$R\text{-}X + R'_3Sn\text{-}Ar\text{-}B(OR'')_2 \xrightarrow{\text{Pd cat.}} R\text{-}Ar\text{-}B(OR'')_2 \quad (3)$$

It is well-known that both carbon–boron and carbon–tin bonds undergo the palladium-catalyzed coupling reaction with aryl or vinyl halides.[13] To accomplish the synthesis

Scheme II



Scheme III



of boron-containing nucleosides, the coupling must take place chemoselectively at the carbon–tin bond of aryltin bearing the boronic group. We initially examined the reaction of **6a** with **1**[14] in the presence of catalytic amounts of palladium tetrakis(triphenylphosphine) ($Pd(PPh_3)_4$, Scheme I). However, neither the desired **7a** nor the starting material **6a** was detected even after a prolong period of reaction (Table I, entry 1). Probably, both C–Sn and C–B bonds of **6a** would be activated with the palladium reagent. After a number of trials, we found that the desired coupling took place in a very high yield with the 2,2-dimethylpropane-1,3-diol-protected derivative **6b** (entry 2). $Pd(PPh_3)_4$ catalyst was much more effective than the other palladium catalysts (entries 3 and 4). The use of a less polar solvent and higher reaction temperature was essential to achieve the coupling (cf. entries 5, 6, and 8). The influence of the protecting group of the sugar portion upon the coupling reaction was also examined. The use of acetonide and methoxymethyl group (entry 7) or the reaction without protection (entry 8) gave poor results, presumably owing to the presence of many oxygen atoms that can be chelated to the catalyst. The sterically bulky *tert*-butyldimethylsilyl group must prevent such coordination of the oxygen atoms to the catalyst.

The aryltin **6b** was prepared from 4-bromophenylboronic acid (**8**).[15] The protection of boronic moiety of **8** with *N*-methyldiethanolamine[16] led to **9** in quantitative yield. Treatment of **9** with butyllithium in THF at −78 °C followed by addition of tributyltin chloride gave **6a** in 53% yield from **8**. The mixing of **6a** and 2,2-dimethyl-

(10) For example: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975.

(11) We attempted the reactions of several carbanions[15] with tributyl borate, but the desired carbon–boron bond formation did not take place in most cases.

(12) The reaction of 6-lithio-2,4-bis(benzyloxy)-1,3-pyrimidine with tributyl borate formed an organoboron compound[6] with a very labile C–B bond.

(13) For the Pd-catalyzed coupling reaction of halides with a C–B bond: (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988**, *344*, C5. For the coupling with a C–Sn bond: (c) Stille, J. K. *Angew Chem., Int. Ed. Engl.* **1986**, *25*, 508. (d) Kosugi, M.; Ishiguro, M.; Negishi, Y.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1511. (e) Kosugi, M.; Sumiya, T.; Ogata, T.; Sano, H.;Migita, T. *Ibid.* **1984**, 1225. (f) Nair, V.; Tuner, G. A.; Chamberlain, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 7233. (g) Nair, V.; Turner, G. A.; Buenger, G. S.; Chamberlain, S. D. *J. Org. Chem.* **1988**, *53*, 3051. (h) Boshmann, F.; Kelly, K. *J. Chem. Soc., Chem. Commun.* **1989**, 532. For the Pd-catalyzed C–C coupling reaction of nucleoside derivatives: (i) Bergstom, D. A.; Ogura, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106.

(14) (a) Tanaka, H.; Hayakawa, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1981**, *29*, 3565. (b) Hayakawa, H.; Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Ibid.* **1987**, *35*, 72.

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(16) Protection of $B(OH)_2$ with *N*-methyldiethanolamine is essential to achieve the lithiation of the bromide **9** chemoselectively without the nucleophilic attack of butyl anion to boron atom, since the boronic moiety and *N*-methyldiethanolamine form an eight-membered ring where the boron vacant orbital is occupied with the lone-pair electrons of the nitrogen atom as shown in **9**. ^1H NMR data of **9** and the following literature supported the presence of boron–nitrogen interaction in the eight-membered ring: Kliegel, W.; Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1988**, *66*, 1091.

propane-1,3-diol in THF followed by concentration of the solvent gave **6b** in 96% yield (Scheme II).

The typical procedure of the coupling reaction is as follows: A solution of the 5-bromouridine derivative 1 (0.3 mmol), the aryltin **6b** (0.34 mmol), and a catalytic amount of $Pd(PPh_3)_4$ (0.015 mmol) in toluene (5 mL) was refluxed with stirring for 1 day under argon atmosphere. The resulting mixture was concentrated in vacuo, and the residue was chromatographed on silica gel to isolate the desired product **7b**.

Next, we applied this procedure to several different nucleoside derivatives (Scheme III). The coupling reaction of the nucleoside derivatives, brominated or iodinated on the sp_2 carbons (**10a**,[6] **11a**,[6] and **12b**[13g]), with the aryltin **6b** also proceeded smoothly under similar conditions, giving the desired coupling products **10c**, **11c**, and **12c**, respectively, in high yields. The compounds **7b**, **10c**, **11c**, and **12c** are storable in the air at room temperature for more than several days. Deprotection of the silyl group and 2,2-dimethylpropane-1,3-diol gave water-soluble nucleosides bearing the $B(OH)_2$ group. These characteristics are highly promising to ^{10}B NCT.

It is now clear that the proper choice of catalyst and protecting group of boronic moiety and the protection of the sugar portion make it possible to combine the bifunctional organometallic compound with the multifunctional nucleoside derivatives. We are now in a position to prepare systematically a number of boron-containing nucleosides. Application of these new ^{10}B carriers for ^{10}B NCT is now in progress.

Acknowledgment. We thank the Iwaki Scholarship Foundation for partial support of this research.

Supplementary Material Available: Full characterization data for **6a**, **6b**, **7b**, **10c**, **11c**, and **12c** are provided along with a detailed procedure for the synthesis of ^{10}B-containing nucleosides (4 pages). Ordering information is given on any current masthead page.

A Regioselective Synthesis of Pyrroles via the Coupling of α,β-Unsaturated Imines with Esters or *N,N*-Dimethylformamide Promoted by $NbCl_3(DME)$

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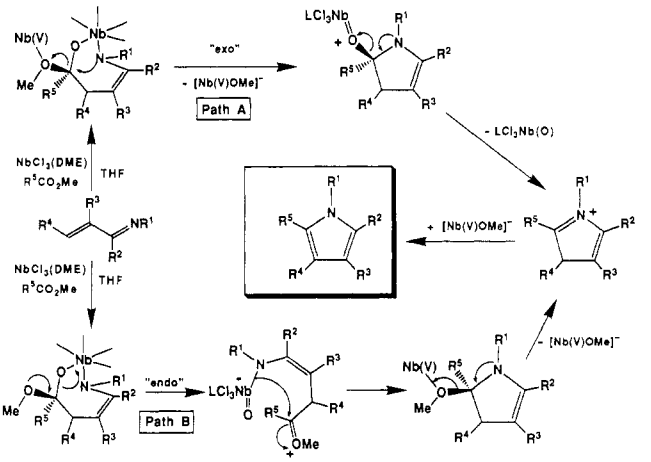
Summary: N-Substituted pyrroles are obtained when α,β-unsaturated imines are combined with $NbCl_3(DME)$ and an ester or *N,N*-dimethylformamide in tetrahydrofuran. The regiochemical outcome of the reaction is completely predictable.

Sir: Recently we described a synthesis of 2-amino alcohols via the coupling of aldimines with aldehydes or ketones promoted by the new reagent $NbCl_3(DME)$.[1] The metallaaziridine intermediate proposed can be considered as an N,C-dianion equivalent (Figure 1). Extension of this formalism to α,β-unsaturated imines suggested that such compounds could function as homoenolate[2] equivalents (Figure 1).[3] The two corresponding organometallic intermediates, C and D, bear structural resemblances to many early metal diene complexes.[4,5] These diene complexes are known to react with esters,[4] unlike the majority of early metal alkyls, including niobium metallaaziridines.[1] Therefore if either intermediate C or D were to react with an ester, an intermediate ketal would form, which could undergo an intramolecular ring closure leading to a pyrrole (Scheme I).[6]

Scheme I



Addition of *N*-allyl-α-methylcinnamaldehyde imine to a solution of $NbCl_3(DME)$ in dry ethyl acetate produced *N*-allyl-2,4-dimethyl-3-phenylpyrrole (Table I, entry 1). A similar reaction using *N,N*-dimethyformamide (DMF) gave *N*-allyl-3-phenyl-4-methylpyrrole (entry 2). *The electrophile need not be employed as the solvent in these re-*

(1) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.

(2) Werstiuk, N. N. In *Umpoled Synthons: A Survey of Sources and Uses in Organic Synthesis*; Hase, T. A., Ed.; John Wiley and Sons: New York, 1987, Chapter 6.

(3) When $NbCl_3(DME)$ and an α,β-unsaturated imine are reacted with an aldehyde or ketone, products resulting from carbon–carbon bond formation between the β-carbon of the imine and the carbonyl carbon are obtained (i.e., 2-aminotetrahydrofurans). Details of these reactions will be described elsewhere.

(4) (a) Yasuda, J.; Nakamura, A. *Angew Chem. Int. Ed. Engl.* **1987**, *26*, 723. (b) Yasuda, J.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120.

(5) Intermediate D has precedent in titanocene chemistry; Cohen, S. A.; Bercaw, J. E. *Organometallics* **1985**, *4*, 1006.

(6) We were led to consider path A from experiments with acylnitriles, which also produce pyrroles. The initially formed positive charge in path B would not be stabilized by the cyano substituent. However, we cannot rule out path B because the acylnitriles could be converted to esters by niobium alkoxides present from some ring opening of THF promoted by either Nb(III) or Nb(V). With respect to the last steps of the mechanism, ^1H NMR studies of the reaction in DMF-d_7 have demonstrated that pyrrole is formed *in situ* (i.e., before hydrolysis).

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