# Synthesis of a Water-soluble *o*-Carbaborane bearing a Uracil Moiety *via* a Palladium-catalysed Reaction under Essentially Neutral Conditions

**Hisao Nemoto,[a] Jianping Cai[b] and Yoshinori Yamamoto*[b]**

[a] *Department of Applied Molecular Science, Okazaki Institute for Molecular Science, Myodaiji 38, Okazaki, Aichi 444, Japan*

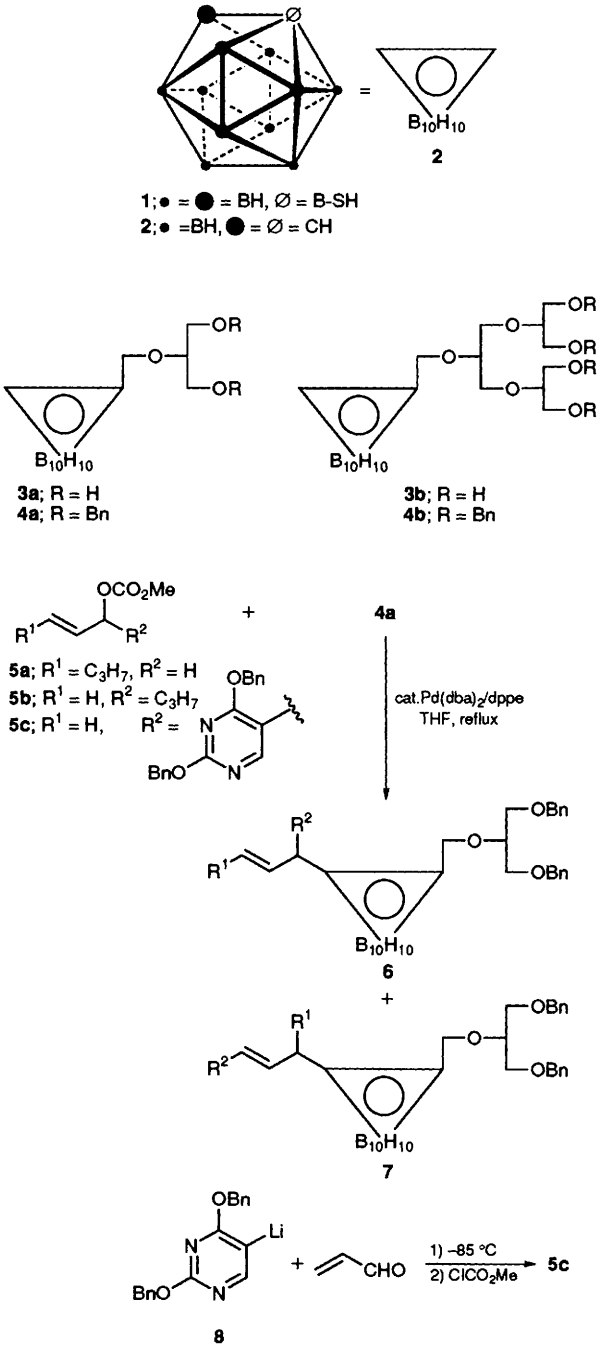
[b] *Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan*

A water-soluble *o*-carbaborane bearing a uracil moiety **10** has been synthesized *via* a palladium-catalysed reaction under essentially neutral conditions.

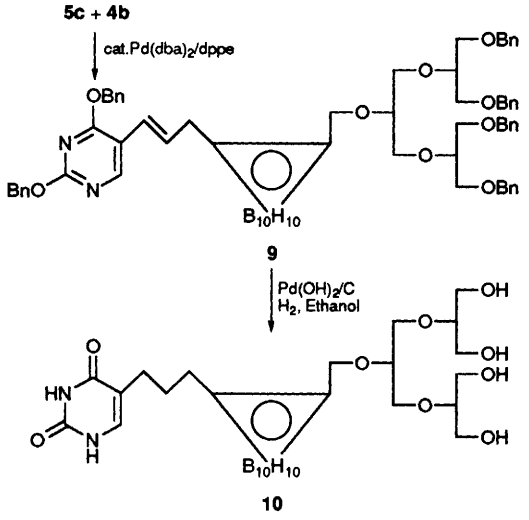
Although the icosahedral boron cluster, dodecaboranethiol **1**, has been used clinically[1] as a boron carrier for boron neutron-capture therapy (BNCT), the efficiency and selectivity of boron uptake by cancer cells still needs to be enhanced. Therefore, a number of synthetic studies of boron carriers[2] containing a similar cluster, *o*-carbaborane **2**, have been reported recently. We previously reported the synthesis of *o*-carbaboranes bearing uracil moieties.[2a,2b] More recently, Takagaki and coworkers have demonstrated that the carbaboranyl uridine ($5B_{10}U$)[2a] is incorporated *ca.* hundred times more efficiently than **1** in human glioma cells.[3] A drawback of $5B_{10}U$ and related carbaborane containing compounds is, however, low water-solubility of those carriers because of high lipophilicity of the *o*-carbaborane cage. In order to enhance the water solubility, we have developed polyglycerols of the cascade type and demonstrated the synthesis of water-soluble *o*-carbaboranes **3** as non-ionic and non-nido type hydrophilic carriers.[4] The next step is to attach a tumor seeking functional group, such as uridine, to the carbaborane framework.

We report here the synthesis of a water-soluble boron carrier bearing a uracil moiety, *via* the palladium-catalysed carbon–carbon bond formation under essentially neutral conditions. The allylation of *o*-carbaboranes with simple allyl carbonate in the presence of palladium catalysts proceeded smoothly to give the allylated carbaboranes in high yields.[5] The palladium-catalysed allylation of ordinary organic molecules with substituted allyl carbonates sometimes affords undesirable results in respect of regiochemistry.[6] It was interesting for us not only from importance of target molecules but also from chemistry of *o*-carbaboranes to know whether the palladium-catalysed allylation with substituted allylic carbonates proceeds regioselectively in the case of *o*-carbaboranes[5] or not. The reaction of two regioisomers **5a** and **5b** with **4a** is shown in Scheme 1.

When **5a** was treated with **4a** in the presence of palladium bis(dibenzylideneacetone) [$Pd(dba)_2$] (10 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe) (20 mol%) in THF at room temp.,† a trace amount of desired compound **6a** was obtained. At reflux, **4a** was completely consumed to give **6a** in 66% yield. No regioisomer **7a** was detected in the crude




**Scheme 1** Palladium-catalysed carbon–carbon bond formation of the *o*-carbaborane derivative **4a**




**Scheme 2** Synthesis of a water soluble *o*-carbaborane-bearing a uracil moiety

reaction mixture. The reaction of **5b** with **4a** under similar conditions gave **7b** as a single regioisomer in 63% yield. Thus, the regiochemistry of allylated products is completely independent from the original structure of the carbonates. Similarly, the uracil precursor **7c** was regiospecifically obtained in 62% isolated yield from **5c** and **4a**. The carbonate **5c** was prepared in 59% yield from 1,2-addition of the aryllithium **8**[7] to acrolein at −85 °C, followed by trapping of the resulting alkoxide with methyl chloroformate at 0 °C.

The reaction of **5c** with **4b** in THF at relux gave **9** in 47% isolated yield (Scheme 2). Treatment of **9** with palladium hydroxide on charcoal in ethanol gave the compound **10** in 75% isolated yield. IR (KBr) 3385, 2920, 2575, 1700, 1660, 1420, 1200, 1100, 1040 $cm^{-1}$; $^1H$ NMr (270 MHz, $CD_3OD$), δ 7.28, (s, 1 H, HC≡C–), 4.17 (s, 2 H, $C_2B_{10}H_{10}$–$CH_2O$–), 3.80–3.25 (m, 15 H, polyglycerol moiety), 2.37–2.22 (m, 4 H, –$CH_2CH_2CH_2$–), 1.62–1.82 (m, 2 H, –$CH_2CH_2CH_2$–); $^{13}C$ NMR (67.5 MHz, $CD_3OD$) δ 166.8 (C=O), 153.5 (C=O), 140.1 (HC=), 113.5 (=C–), 82.9 (–$CB_{10}H_{10}$–), 80.7 (–$B_{10}H_{10}$-C–$CH_2$–O–), 80.5 (–$B_{10}H_{10}C$–), 79.7 (–OCH–$CH_2O$–C–), 71.3, 71.2 (–O–CH–), 62.5 (–$CH_2OH$), 35.3, 29.9, 27.0 (–$CH_2CH_2CH_2$–).

It is now clear that the palladium-catalysed allylation reaction of *o*-carbaboranes proceeds smoothly not only with allylic carbonate derivatives bearing large substituents, but also with *o*-carbaboranes bearing cascade polyol units. The synthesis of a water-soluble *o*-carbaborane-bearing uracil moiety was accomplished by the palladium method. The biological properties of **10** are now under investigation.

*Received, 15th November 1993; Com. 3/06813G*

## Footnote

† The simple allylation of *o*-carbaboranes proceeded very well at room temperature.[5]

## References

1 H. Hatanaka, K. Sano and H. Yasukochi, in *Progress in Neutron Capture Therapy for Cancer*, ed. B. J. Allen, D. E. Moore and B. V. Harrington, Plenum, New York, 1992, p. 561; M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950.

2 (*a*) Y. Yamamoto, T. Seko, H. Nakamura, H. Nemoto, H. Hojo, N. Mukai and Y. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 1992, 157; (*b*) Y. Yamamoto, T. Seko, H. Nakamura and H. Nemoto, *Heteroatom Chem.*, 1992, **3**, 239; (*c*) H. Kets, W. Tjarks and D. Gabel, *Tetrahedron Lett.*, 1990, **31**, 4003; (*d*) J. L. Maurer, F. Berchier, A. J. Serino, C. B. Knobler and M. F. Hawthorne, *J. Org. Chem.*, 1990, **55**, 833; (*e*) S. B. Kahl, M.-S. Koo, *J. Chem. Soc., Chem. Commun.*, 1990, 1769; (*f*) A. K. M. Anisuzzaman, F. Alam and A. H. Soloway, *Polyhedron*, 1990, **9**, 891.

3 M. Takagaki, Y. Oda, Z. H. Zhen and H. Kikuchi, personal communication.

4 H. Nemoto, J. G. Wilson, H. Nakamura and Y. Yamamoto, *J. Org. Chem.*, 1992, **57**, 435.

5 H. Nemoto, F-G. Rong and Y. Yamamoto, *J. Org. Chem.*, 1990, **55**, 6065. The previous allylation of carbaboranes was carried out with those having an electron withdrawing group at the carbon terminus.

6 Regiochemistry of allylations *via* palladium catalysts depends upon the substrates, leaving groups, phosphine ligands, and nucleophiles. J. Tsuji, *Pure Appl. Chem.*, 1982, **54**, 197.

7 Preparation of **8**: R. F. Schinazi and W. H. Prusoff, *J. Org. Chem.*, 1985, **50**, 841.